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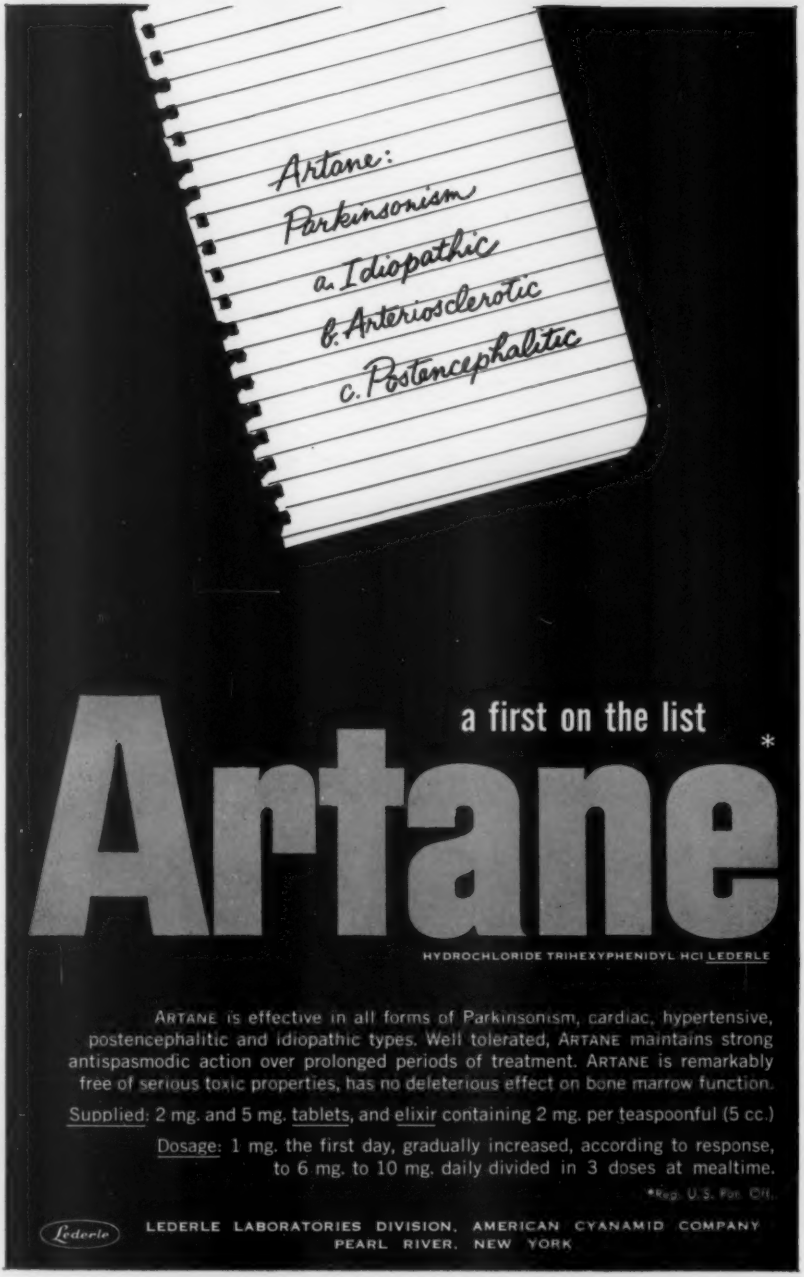
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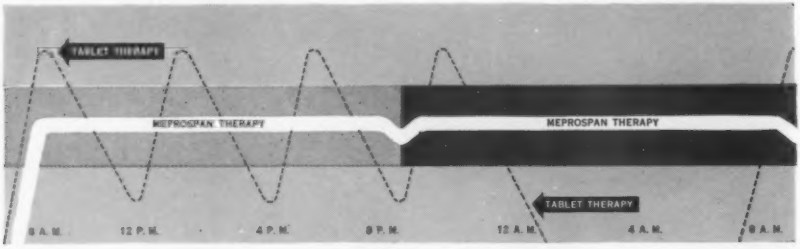

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Volume 8 **Neurology** Number 6

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JUNE 1958 • *Contents*

Focal Seizures Due to Chronic Localized Encephalitis 435
THEODORE RASMUSSEN, M.D., JERZY OLSZEWSKI, M.D. AND DONALD LLOYD-SMITH, M.D.

Comparative Effects of Relaxant Drugs on Human Skeletal Muscle Hyperactivity 446
FRANCIS A. VAZUKA, M.D.

Spinal Fluid Protein in Tumors of the Sellar Region 455
LOUIS BAKAY, M.D.

Alcoholic Gasserian Injection for Relief of Tic Douloureux Preliminary Report of a Modification of Penman's Method 461
ARTHUR ECKER, M.D. AND THEODORE PERL, M.D.

Relationship of Dystrophia Myotonica (Myotonic Dystrophy) and Myotonia Congenita (Thomsen's Disease) 469
J. E. CAUGHEY, M.D., F.R.C.P., F.R.A.C.P.

Localization Within the Amygdaloid Complex of Anesthetized Animals 477
CHARLES D WOOD, Ph.D., BYRON SCHOTTELIUS, Ph.D., LAWRENCE L. FROST, Ph.D. AND MAITLAND BALDWIN, M.D.

Vertebral Deformities and Other Abnormalities in Charcot-Marie-Tooth Disease 481
CASWELL K. SMITH, M.D.

(Continued on next page)

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Contents — *Continued*

The Narcolepsy Syndrome 487
WALTER GANADO, B.Sc., M.D., M.R.C.P.

Subcutaneous Hemorrhages in Multiple Sclerosis 497
ROY L. SWANK, M.D.

Obituary
J. Godwin Greenfield 1884-1958 499

Case Report
Asian Influenza Virus as the Cause of Acute Encephalitis 500
WILLIAM E. BELL, M.D., A. P. McKEE, M.D. AND R. A. UTTERBACK, M.D.

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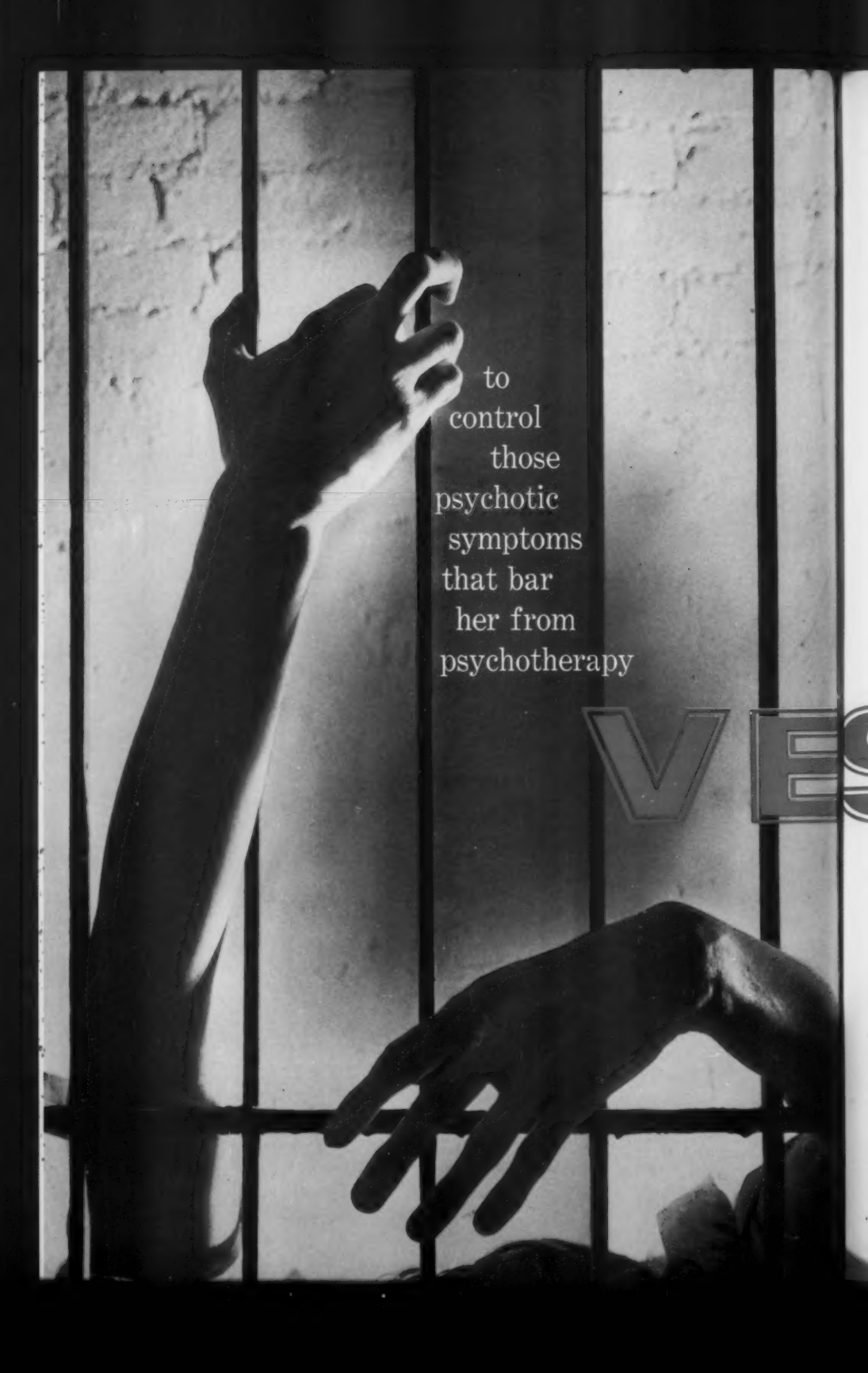
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Neurology Volume 8 • Number 6

Focal seizures due to chronic localized encephalitis

Theodore Rasmussen, M.D., Jerzy Olszewski, M.D.* and Donald Lloyd-Smith, M.D.

OCCASIONAL SPECIMENS of scarred, atrophic brain removed for the relief of focal cerebral seizures at the Montreal Neurological Institute have shown striking perivascular collections of round cells, particularly in less severely damaged areas of these specimens. In the past this perivascular cuffing has been attributed to the effect on the brain of recurring seizures, with recognition, however, that this was a rather unsatisfactory explanation since the great majority of surgical specimens removed from patients with equally frequent focal seizures do not show this change. Histologic studies of surgical specimens from three children recently operated upon for intractable focal seizures suggest that this microscopic picture may indicate the presence of an unsuspected, more or less localized, chronic encephalitis that has smoldered along over a period of years. The clinical and histologic data on these three children will be reported in some detail.

The most complete study from the pathologic standpoint was made in the last of the three patients to appear. This case will be discussed first, since it seems to clarify interpretation of the train of events in the other two.

CASE REPORTS

Case 1. An 18 month old boy developed seizures following an infected scratch behind the right ear. Focal right-sided seizures became increasingly frequent, despite maximal doses of anticonvulsants. Removal of the left frontal lobe, carried out six months after the onset of seizures in a fruitless attempt to stop them, provided an opportunity to compare the microscopic picture at that time with that shown at autopsy three and a half months later.

Birth and early development of this child were normal, and there were no significant illnesses until April 1955 at 18 months of age, when the parents noted a scratch behind the right ear. The following day swelling in this region was noted and the temperature rose to 104° F. The temperature subsided the next day after administration of penicillin, but the swelling behind the ear continued to discharge bloody fluid for one week.

The child seemed entirely well for two months, but in July he became unusually irritable one day and vomited the following morning. That afternoon he seemed dizzy and soon after was noted to stare and salivate; he then developed clonic jerking movements of the right side of the body. The clonic seizure soon became generalized and persisted for an hour before the convulsion was stopped by administration of chloroform.

A similar attack occurred a month later in August 1955, and from then on milder right-sided seizures recurred several times daily. During the next three months his usual quiet, pleasant behavior changed and he became somewhat irritable and destructive. During this period his parents felt that his speech was becoming somewhat less clear than it had been.

In November the right arm became completely useless and hung limply by his side for three days.

From the department of neurology and neurosurgery, McGill University and the Montreal Neurological Institute, Montreal, Quebec, Canada.
*Present address: Laboratory of Experimental Neuropathology, College of Medicine, University of Saskatchewan, Saskatoon, Canada.

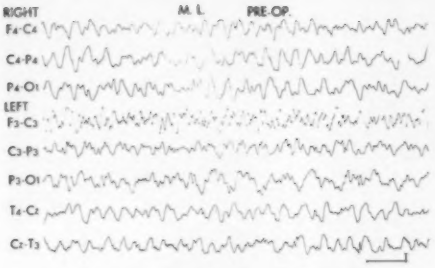

FIG. 1. *Case 1.* Sample from an electroencephalogram made during the first week in hospital. Horizontal scale indicates 1 second, vertical scale represents 100 microvolts.

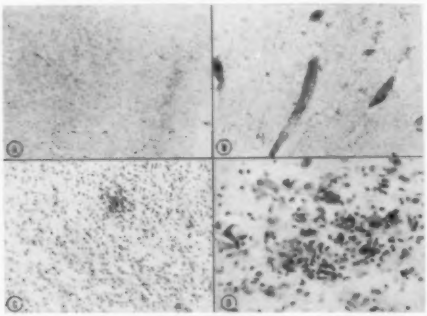

FIG. 2. *Case 1.* Surgical specimen from left frontal lobe. *A.* Nissl stain, 165x. *B.* Nissl stain, 400x. *C.* Nissl stain, 55x. *D.* Gold chloride sublimate impregnation, 165x.

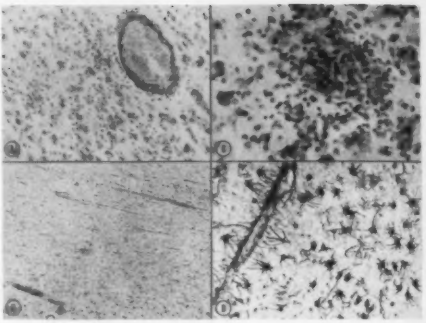

FIG. 3. *Case 1.* Sections from autopsy. *A.* Right frontal lobe, Nissl stain, 55x. *B.* Left frontal lobe, Nissl stain, 55x. *C.* Left cuneus, Nissl stain, 165x. *D.* Left frontal lobe, Nissl stain, 400x.

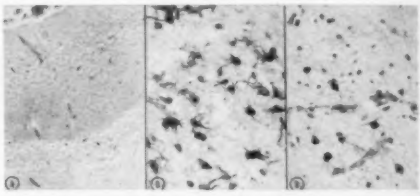

FIG. 4. *Case 1.* Sections from autopsy. *A.* Left cuneus, hematoxylin-phloxin-safranin stain, 55x. *B.* Left central region, gold chloride sublimate impregnation, 400x. *C.* Right central region, gold chloride sublimate impregnation, 400x.

Strength then returned in the arm, but his gait gradually became unsteady.

He was admitted to the Montreal Neurological Institute December 8, 1955, five months after his first seizure. He was a cooperative two year old boy, talking and playing normally between frequent major and minor right-sided seizures. There was a slight but definite right hemiparesis. He was somewhat dehydrated, but once that was corrected the urinalysis and white blood cell count were normal. There was a moderately severe hypochromic anemia. The spinal fluid findings were normal, as were skull and chest roentgenograms and a pneumoencephalogram.

An electroencephalogram showed widespread slow-wave abnormalities from both sides of the head, with frequent seizure discharges in the left frontocentral region (figure 1).

The patient continued to have many right-sided seizures daily, despite maximal doses of Dilantin, phenobarbital, Tridione, Mysoline, Mesantoin, and bromides. At times paraldehyde was necessary to stop episodes of status epilepticus. Sleep for several hours each day induced with Avertin given rectally failed to control the seizures which recurred each time as he awakened. Between attacks, however, he was able to play with his toys if not too heavily medicated.

The slight right hemiparesis gradually became more marked. On January 10, 1956, six months after the onset, he was operated upon and the right frontal lobe was removed in a futile effort to interrupt the almost daily episodes of status epilepticus which were thought to be producing the slowly progressive hemiparesis. The cortex appeared grossly normal, but the cortical electroencephalogram showed epileptiform activity throughout the entire exposed area, most marked anteriorly. The postoperative cortical electroencephalogram showed the epileptiform abnormality persisting unchanged in the central and parietal regions.

Seizures recurred as he awakened from the anesthetic and continued as before operation. A postoperative electroencephalogram two weeks later showed the same diffuse slow-wave abnormality as before, with most marked epileptiform activity in the left central region. Bromides, administered until the blood level reached 280 mg. per cent,

lessened the attacks little if at all. Keeping the child asleep with paraldehyde was the only effective way of stopping the attacks. For several weeks he was allowed to wake up two or three times each day to eat but he often vomited his meals with a seizure; it finally became necessary to feed him by stomach tube while he was asleep in order to maintain adequate nutrition. His course had been quite afebrile before operation and during the first two postoperative months. In March 1956 salivation with the seizures became an increasing problem. Despite the tracheotomy which was carried out at this time, it was difficult to keep his lungs clear. The seizures continued, his general condition gradually deteriorated, and he died April 24, 1956, three and one-half months after operation and nine months after his first seizure.

The initial spinal fluid examination in December 1955 showed 3 cells per cu.mm. and 18 mg. per cent protein. Because histologic examination of the surgical specimen removed in January 1956 showed evidence of encephalitis (figure 2), the cerebrospinal fluid was examined periodically during his postoperative course, starting four weeks after operation when it was felt that any pleocytosis due to the operation itself would have subsided completely. Weekly examinations in February, four to eight weeks after operation, showed 20 to 55 white cells per cu. mm., mainly polymorphonuclear cells in the first two specimens and mainly mononuclear cells in the next three specimens. The protein levels varied from 66 to 98 mg. per cent. The colloidal gold curve on February 29 was 255543200. In March, two months after operation, despite continuation of the seizures and deterioration in his general condition, two examinations a week apart revealed only 2 and 6 lymphocytes per cu. mm. and the protein, sugar, and chlorides were normal. On April 23, the day before death, the spinal fluid showed 2 lymphocytes per cu. mm. and a protein of 17 mg. per cent.

Pathology

In the surgical specimen removed six months after his first seizure and three and one-half months before death, there were multiple small accumulations of inflammatory cells scattered in a random manner throughout the cortex and white matter but less numerous in the latter (figure 2 A and C). They were composed of small round cells and microglia with occasional polymorphonuclear cells (figure 2B). There was a small amount of perivascular cuffing, predominantly in the cortex, but present also in the white matter (figure 2A and C). The meninges were thick and infiltrated by inflammatory cells, predominantly lymphocytes. There were marked hypertrophy and hyperplasia of astrocytes diffusely throughout both the gray and white matter (figure 2D).

Autopsy examination was limited to the brain, which weighed 795 gm. and appeared grossly normal except for the surgical amputation of the left frontal lobe. Blocks were cut from various areas of the convexities and basal ganglia of the two cerebral hemispheres, cerebellum, pons, and medulla and stained by both tinctorial and metallic methods.

Sections from the right hemisphere were normal, except for the presence of a few small round cells in the perivascular spaces around some of the larger vessels and occasional round cells in the leptomeninges (figure 3A).

Sections from the left hemisphere showed intensive perivascular cuffing by round cells in both the cortex and white matter in all areas, similar to that seen in the surgical specimen (figure 3B). There were numerous diffuse and patchy areas of infiltration of the cortex and white matter by inflammatory cells, predominantly microglia and small round cells with occasional polymorphonuclear cells (figure 3C and D). Red cells were numerous in all regions, especially in the cortex. Numerous areas showed laminar loss of nerve cells in the fifth and sixth layers, with spongy degeneration (figure 4A). The astrocytes were hypertrophied and increased in number as compared with the right hemisphere (figure 4B and C).

There was a similar but less marked inflammatory process in the basal ganglia on the left, while the corresponding region on the right was normal, except for the presence of a few compound granular corpuscles and an occasional round cell around a few of the larger vessels.

The pons, medulla, and cerebellum were normal, except for the presence of a few inflammatory cells in the leptomeninges and a slight reduction in number of the Purkinje cells.

Summary of Pathologic Findings

In the surgical specimen there were many nodules of inflammatory cells distributed in a random manner throughout the cortex and to a lesser extent in the white matter. There was minimal but definite perivascular cuffing in both the cortex and white matter, less marked in the latter. The cortex and white matter were well preserved otherwise.

At postmortem examination three and one-half months later, there was early laminar spongy degeneration in the cortex with intense perivascular cuffing and, as in the surgical specimen, diffuse infiltration of inflammatory cells in both gray and white matter. These changes were limited almost exclusively to the left cerebral hemisphere.

Comment

To summarize findings in this patient, two months after an apparently insignificant and perhaps unrelated skin infection behind the right ear, an encephalitis developed whose only manifestation during the first few months was frequently recurring focal seizures. Two or three months after the onset his behavior gradually became more irritable and his speech a little less clear. Four months after the onset,

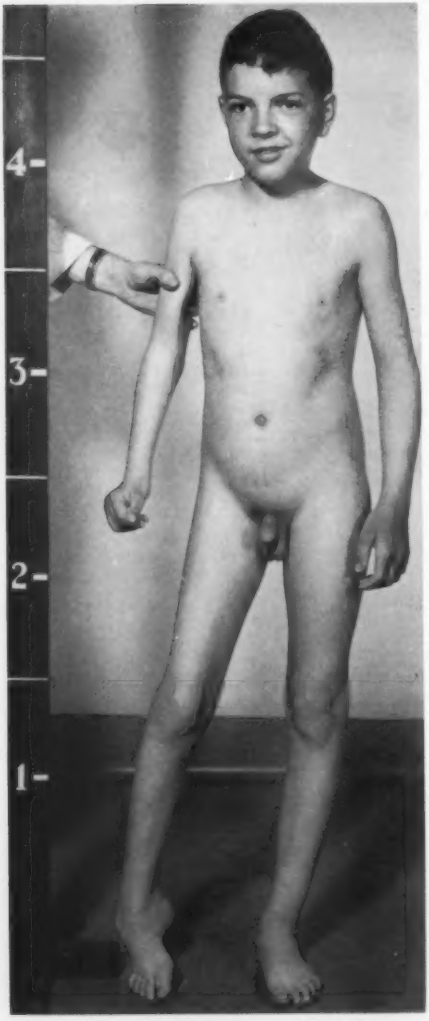

FIG. 5. *Case 2.* Patient at age 11 years, six years after onset of his illness.

a slight but progressive right hemiparesis appeared. Death ensued nine months after the onset. Despite the progressive character of the disease and ultimately fatal outcome, it remained almost completely limited to the left cerebral hemisphere.

Histologic changes consisted of subacute and chronic encephalitis, with intense astrocytic reaction and early laminar spongy degeneration of the cerebral cortex. In view of the extensiveness of the inflammatory process demonstrated in the autopsy studies, it is of particular interest that the spinal fluid was entirely normal during the four and one-half month period of hospitalization, except for the four weekly examinations made during his second postoperative month. It seems unlikely that the pleocytosis and elevation of protein found in these specimens could be due to reaction from the operation, but this possibility cannot be ruled out completely. Unfortunately no spinal fluid examinations were made during the first five months of the illness. Our initial impression that the frequent focal seizures themselves were responsible for the slowly progressive right hemiparesis is doubtless incorrect. In retrospect, it seems clear that an encephalitis was present and was responsible for the hemiparesis as well as for the seizures.

Case 2. An 11 year old boy (figure 5) was studied thoroughly over a period of several years at the Sick Children's Hospital in Toronto. Following the onset of focal seizures at age five, he developed two episodes of status epilepticus which left him with a permanent right hemiparesis. Frequent focal seizures persisted, ultimately requiring left hemicorticectomy at age 11 years.*

This boy had a normal birth and early development, the only illness being measles at one year of age. In 1949 at age five, without any antecedent illness or apparent cause, episodes of twitching of the right side of the face appeared and recurred many times daily. The twitching soon spread to involve the right arm and leg as well. A month or so after the onset, a series of generalized seizures occurred in which he was unconscious for several hours. On awakening there was a marked weakness of the right arm which proved to be permanent. A similar convulsive episode two months later was followed by a persisting weakness of the right leg as well. There was apparently no speech disturbance on either of these occasions, despite the fact he had been considered to be right-handed.

Following each of these convulsive episodes he was hospitalized in Toronto and studied completely, and on each occasion the spinal fluid examination and pneumoencephalogram were normal (figure 6A). The seizures continued essentially unchanged. In April 1951, two years after the onset, a repeat pneumogram showed for the first time slight but definite enlargement of the left lateral ventricle (figure 6B). An exploratory

*We are indebted to Dr. W. A. Hawke and Dr. W. S. Keith at the Sick Children's Hospital in Toronto for providing us with their detailed data and roentgenograms which were of great help in analyzing case 2.

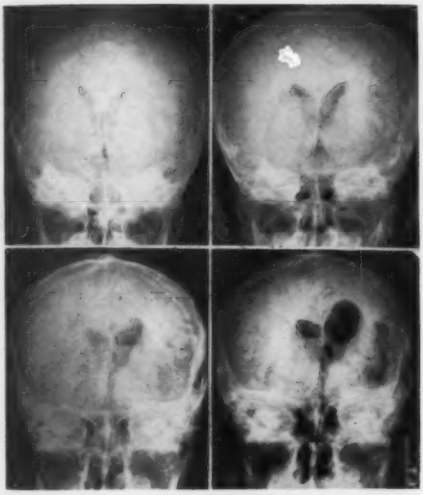

Fig. 6. *Case 2.* Pneumoencephalograms. *A.* 1949, age five years. *B.* 1951, age seven years. *C.* 1954, age ten years. *D.* 1955, age 11 years.

craniotomy and cortical biopsy were then carried out. No gross lesion was seen and the biopsy specimen on histologic examination was reported as showing only diffuse gliosis of moderate degree. The spinal fluid was examined after this operation and showed a total protein of 22 mg. per cent, negative Wassermann reaction, and a normal colloidal gold curve.

The right hemiplegia persisted and the right-sided seizures continued as often as every five minutes, with the longest seizure-free intervals rarely exceeding one or two days. In July 1954 the pneumogram was repeated again, and showed more marked evidence of atrophy of the left cerebral hemisphere (figure 6C). During the ensuing year the patient was confined to bed most of the time due to frequency of the seizures, and as a result he developed contracture of the right ankle in a position of equinovarus.

On admission to the Montreal Neurological Institute in April 1955 he was a quiet, alert, well-behaved boy, with a marked spastic right hemiplegia (figure 3) and a complete right homonymous hemianopsia. Only slight voluntary wrist movements were present; there were strong mass flexion movements at the fingers but no individual finger movements and no voluntary movement at the ankle or toe joints. There was moderate smallness of both the right arm and leg. There was reduced appreciation of pain and light touch over the right half of the body, absent joint sense in the right hand and foot, reduced vibration sense in the right arm and leg, and a gross defect in two-point discrimination and figure writing on the right hand and foot.

Many seizures were witnessed, all starting with a sensory aura on the right, usually appearing first in the leg, occasionally in the arm, rarely starting in the face. This sensory aura was followed by unresponsiveness, a bending forward at the waist, a tonic elevation of the right arm, and then clonic jerking of the right arm as the head and eyes turned, usually to the right, but occasionally to the left. Often there was also twitching of the right side of the face and right leg. He spoke promptly and normally immediately after the attacks were over.

Psychologic testing showed an I.Q. rating of 53 on the Wechsler intelligence scale for children, with a verbal I.Q. of 61 and a performance I.Q. of 51. On casual conversation, however, he did not impress one as being mentally retarded to this degree.

Blood, urine, and spinal fluid findings were normal. The skull roentgenogram showed only slight smallness of the left hemicranium, but the pneumogram showed evidence of marked destruction of the left hemisphere, with only slight enlargement of the right lateral ventricle anteriorly (figure 6D). The electroencephalogram showed fairly marked slow-wave abnormality bilaterally, with focal epileptogenic activity in the left frontal, left temporal, and right parietal areas.

On May 10, 1955 a left hemicorticectomy was carried out. The hemisphere was composed of small, somewhat yellowed gyri of moderately increased firmness, but there were no areas of gross destruction. The hemisphere was removed completely peripheral to the striatum and thalamus (figure 7).

He had a minor seizure the first postoperative day and a low grade temperature elevation during the first two postoperative weeks; otherwise the postoperative course was uneventful. There was no speech disturbance; motor function in the right leg returned to the preoperative level by the end of the first postoperative day and in the right arm by the fourth postoperative day. The postoperative electroencephalogram showed the usual posthemicorticectomy flat, low voltage record on the left, with the same pattern on the right as was seen preoperatively, consisting of some slow-wave abnormality with sporadic sharp waves in the right parietal region.

Three weeks postoperatively, just before discharge, psychologic tests showed the I.Q. had risen slightly from 53 to 58, probably due to some improvement in attention span.

In September 1955, four months after operation, surgical correction of the equinovarus deformity was carried out at the Sick Children's Hospital in Toronto. Psychometric examination at that time showed no marked change from the preoperative tests carried out there the year previously.

He has remained seizure-free since his first postoperative day and has received no anticonvulsant medication since operation. Eight months after operation he started going to school for the first

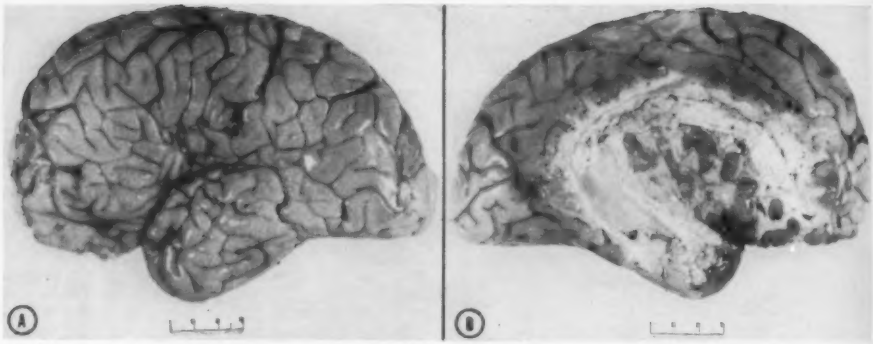

FIG. 7. *Case 2.* Surgical hemicorticectomy specimen. *A.* Lateral surface. *B.* Medial surface.

time in his life, attending a class for slow learners. At the latest follow-up report one year and eight months after operation, he was reported to be making good progress in school work and getting along happily with his schoolmates.

Pathology

The convolutional patterns of the specimen showed markedly narrowed gyri in the Sylvian region (figure 7), with the remaining convolutions slightly narrow and most of them moderately increased in consistency. On histologic examination there were areas of spongy degeneration of the cortex distributed irregularly over the entire hemisphere, but most marked in the Sylvian region. In some areas this spongy degeneration occupied the whole thickness of the cortex except the first layer. In these regions the nerve cells were markedly reduced in number and the tissue consisted of a loose network of glial fibers with small microscopic cysts between them (figure 8A). In areas where the cortex was better preserved, a few vessels showed well marked perivascular cuffing by small round cells (figure 8B). Scattered throughout the cortex were a few inflammatory nodules made up of small round cells and microglia. In other areas the cortex was diffusely infiltrated with these inflammatory cells and showed beginning spongy destruction. Similar inflammatory changes were present in the white matter, marked in some areas and minimal in others. There were marked hyperplasia and hypertrophy of the astrocytes present diffusely throughout the gray matter, and to a lesser extent in the white matter (figure 8C). The myeline in the white matter was well preserved except in the convolutions which were markedly degenerated.

Pathologic Summary

In the hemicorticectomy specimen which was removed six years after the onset of the illness, there was evidence of a chronic encephalitic process in the gray and white matter. In many regions the cortex was so severely damaged that it was

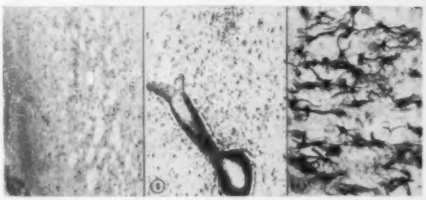

FIG. 8. *Case 2.* Surgical specimen. *A.* Left parietal lobe, hematoxylin-phloxin-safranin stain, 55x. *B.* Left frontal lobe, Nissl stain, 165x. *C.* Left central area, gold chloride sublimate impregnation, 400x.

reduced to a narrow layer of spongy glial tissue. In better preserved areas, chronic inflammatory cells formed cuffs around blood vessels and were scattered diffusely throughout the tissue.

Comment

This patient was actually the first one encountered. From the clinical standpoint it was our impression preoperatively that his history represented a typical instance of a child developing postictal hemiplegia as a result of seizures due to some pre-existing fixed lesion, such as a cerebral cicatrix or some metabolic disorder. The histologic evidence of an inflammatory process came as a complete surprise, in view of the lack of any of the usual signs of encephalitis in this patient's clinical story. There was a history of measles at age one, but no infection of any kind was reported at or just before the onset of the seizures at age five. Pathologically the lesions were more advanced than in the first patient, showing more destruction and less active inflammatory reaction, but the latter was identical in type and distribution.

FIG. 9. *Case 3.* Pneumoencephalograms. *A.* 1951, age three and one-half years. *B.* 1952, age five years. *C.* 1956, age eight years.

Case 3. An eight year old boy developed his first seizure with a mild attack of "flu" at age two and one-half. Left-sided seizures persisted and after a year a slowly progressive left hemiparesis developed. Right frontal lobectomy at age six failed to stop the seizures or the progressive hemiparesis. Right hemicorticectomy was carried out five years after the onset.

This patient* showed no evidence of birth injury and developed normally until age three and one-half. At this time he had a mild attack of "flu," for which the family physician was called to the house. While the physician was making his examination, the boy had a generalized convulsive seizure. He was hospitalized for a few days and then discharged, apparently well.

Two months later in March 1951, he developed recurring left-sided clonic seizures of one minute's duration. He was again hospitalized and studied in his home city of Columbus, Ohio. Clinical neurologic data, skull roentgenograms, and pneumogram were all normal (figure 9A). The spinal fluid showed three polymorphonuclear cells and five lymphocytes per cu. mm. and a protein of 23 mg. per cent. The electroencephalogram showed a moderately severe generalized dysrhythmia, with focal abnormalities in the right occipitoparietotemporal area. Since the air studies showed no evidence of an expanding lesion, the consulting neurosurgeon suggested, on the basis of electroencephalographic and clinical evidence, that the child had a low grade encephalitis. On Dilantin and phenobarbital, however, the patient was seizure-free and apparently well for the next year.

In February 1952, at age four and one-half, one year after the first attack, the seizures recurred and persisted, occurring five to six times daily. He became hyperactive and a moderate behavior problem, and gradually developed slight weakness of the left arm and leg. He was studied again in October 1952. The spinal fluid at this time showed four polymorphonuclear cells per cu. mm., a trace of globulin, and a normal colloidal gold curve. At this time, nearly two years after his initial "flu" and convulsion, he was referred to one of the authors at the University of Chicago Clinics for consideration of surgical therapy of the seizures, in the hope of preventing progression of hemiparesis.

The patient exhibited at this time (November 1952) a mild left hemiparesis with appropriate reflex changes. The blood, urine, and spinal fluid were all normal, the latter showing no cells, negative Pandy, protein of 22 mg. per cent, and chlorides 123 mEq. per liter. The pneumogram, which had been normal a year and a half earlier, showed moderate dilatation of the body and frontal horn of the right lateral ventricle, with a 5 mm. shift of the septum pellucidum toward this side; also there was clear evidence of enlargement of the subarachnoid spaces over the right frontal region (figure 9B). The posterior half of the right lateral ventricle was similarly enlarged. The electroencephalogram showed diffuse bilateral slow-wave abnormality, most marked in the right frontal and central region, and also bilaterally synchronous sharp waves in both frontal regions, with the greatest amplitude and sharpest wave forms on the right side. We concluded that a progressive atrophic process was present and surgery not indicated unless the process became stationary and more localized.

The left hemiparesis gradually increased until he was confined to a wheelchair most of the time. The left-sided seizures became still more frequent until it was deemed necessary in October 1953, nearly three years after the onset of the illness, to remove the right frontal lobe in an effort to prevent recurring episodes of status epilepticus. Histologic examination of the specimen removed sug-

*Case 3 was referred by Dr. Kenneth Abbott, Columbus, Ohio, to whom we are indebted for providing detailed clinical data and roentgenograms of his repeated studies, as well as microscopic slides from the frontal lobectomy.

gested the diagnosis of encephalitis (see discussion of pathology).

Following frontal lobectomy, the seizures became less frequent for a time and strength in the leg improved slightly so that he could walk, although with a hemiplegic limp. During the next year the seizures again increased in frequency and the hemiparesis progressed.

He was referred back for further consideration of surgical therapy for his seizures, and was admitted to the Montreal Neurological Institute in March 1956. Minor seizures were occurring every few minutes, in which he would stop talking, slump forward, and show twitching movements of the left arm and left side of the face. It was necessary to keep him in bed or tied in a wheelchair, wearing a football helmet to prevent banging his forehead constantly in his seizures. He was dull in appearance, with marked gingival hypertrophy from heavy Dilantin medication. There was much salivation and his respirations were noisy with loud moist rales and rhonchi. He was able to talk during some of the shorter spells; during the larger attacks he would be unresponsive for a minute or two and the clonic movements would involve the entire left side of the body.

There was smallness and a moderately spastic paralysis of the left extremities with appropriate reflex changes. It was not possible to examine the sensory system adequately, but appreciation of pinprick seemed reduced and delayed over the left half of the body.

The urine, blood, and spinal fluid were normal. Skull films showed a small skull, with the internal diameters unchanged from films made three and a half years earlier, suggesting there had been little or no brain growth during this time. There was a slight selective smallness of the right side of the calvarium, in addition.

The pneumogram showed a marked increase in dilatation of the right lateral ventricle as compared with the 1952 examination two and one-half years earlier, with a marked shift to the right of the septum pellucidum and third ventricle (figure 9C). The changes were almost as marked in the posterior part of the ventricular system, and the left lateral projection showed that the right temporal horn was also proportionally enlarged. The electroencephalogram showed evidence of a large active epileptogenic area throughout the right central, parietal, and posterior temporal regions (figure 10A).

On March 13, 1956, five years after the onset and two and one-half years after the right frontal lobectomy, he was operated upon again and a wide exposure made of the right hemisphere behind the area of the previous frontal removal (figure 11). There was marked thickening of the arachnoid, with adhesions to the dura most marked over the central region adjacent to the site of the previous operative exposure. The convolutions were all small and of increased consistency, but there were no areas of gross destruction of brain, except at the site of the previous frontal lobectomy. The cortical electroencephalogram showed high amplitude spikes coming from all exposed areas. A complete right hemicorticectomy was carried out, removing the entire hemisphere peripheral to the striatum and thalamus.

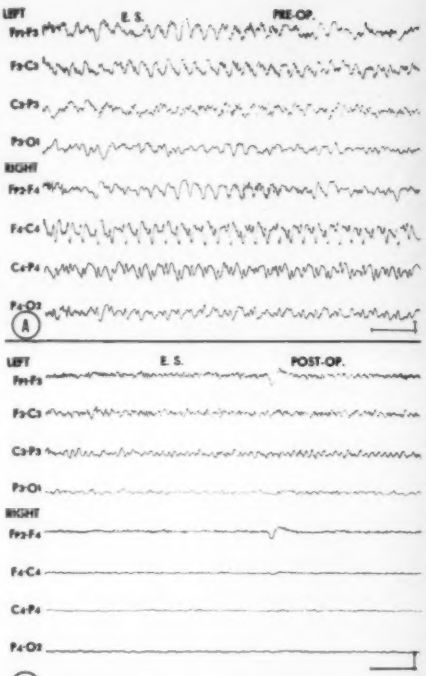

FIG. 10. *Case 3.* Electroencephalograph samples. *A.* Before right hemicorticectomy. *B.* After hemicorticectomy. Note improvement in record from left (unoperated) hemisphere. Horizontal scale indicates 1 second, vertical scale represents 100 microvolts.

Postoperatively he had a low grade elevation of temperature for the first week, but no seizures except for a 10 second episode of twitching of the left arm on the first postoperative day. By the third postoperative day he was much more alert than he had been preoperatively. On discharge three and one-half weeks after operation, he was walking with less support than on admission. Some voluntary movement at the left elbow had returned and there was some reduction in spasticity; otherwise the left hemiplegia was essentially unchanged. It was now possible to test sensation a little more completely. Appreciation of light touch was markedly reduced over the left side. Pinprick was felt but reduced and was localized poorly on the left side, whereas it was localized accurately on the right.

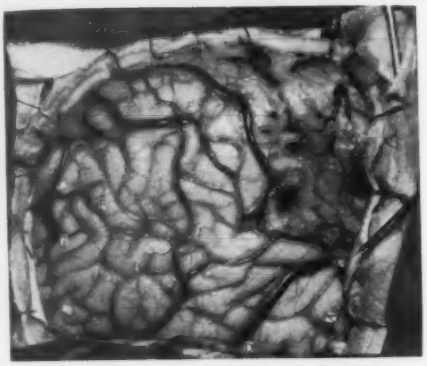

FIG. 11. *Case 3.* Operative photograph. Letters indicate areas of maximum abnormality in cortical electrogram. Letters *A* and *D* are on temporal lobe, *C* and *G* on occipital lobe, *E* and *F* on parietal lobe.

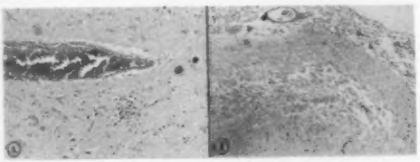

FIG. 12. *Case 3.* Sections from right frontal lobe (1953). *A.* Hematoxylin-eosin stain, 165x. *B.* Hematoxylin-eosin stain, 55x.

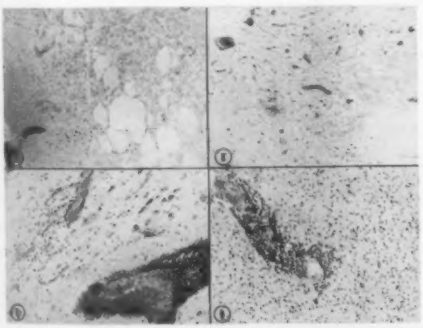

FIG. 13. *Case 3.* Sections from hemicorticectomy specimen (1956). *A.* Central area, hematoxylin-phloxin-safranin stain, 55x. *B.* Parietal lobe, hematoxylin-phloxin-safranin stain, 55x. *C.* Central area, hematoxylin-phloxin-safranin stain, 165x. *D.* Central area hematoxylin-phloxin-safranin stain, 165x.

An electroencephalogram three weeks after operation showed marked improvement, with a flat record over the right side and normal activity from the left hemisphere, except for some trains of low amplitude 4 per second waves recorded from the left central region (figure 10B).

Two months after operation he was walking without assistance, but with a hemiplegic gait. There was marked improvement in mentality, alertness, and personality. At latest report, one year and four months after operation, he is still seizure-free and taking only a small daily dose of phenobarbital. He walks well, with the limp lessened considerably by the use of an ankle brace. He has started going to school and is beginning to read and write a little.

Pathology

Specimens from the frontal lobe removed in 1953 showed a scattering of glial nodules and definite perivascular round cell infiltration in both gray and white matter (figure 12A). There were also prominent patches of laminar necrosis and focal cortical atrophy (figure 12B).

The hemicorticectomy specimen removed two and one-half years later showed more severe tissue destruction and less extensive inflammatory changes, as compared with the earlier frontal lobe specimens. In the more rostral part of the hemicorticectomy specimen, most of the cortex was surrounded by dense fibrous astrocytic tissue in which only an occasional nerve cell persisted (figure 13A). The first cortical layer was spared and showed the presence of gemistocytic astrocytes. The white matter beneath these areas of spongy degeneration showed perivascular cuffing by small round cells and intense gliosis. Occasionally a relatively well preserved gyrus was adjacent to one badly damaged. More caudally in the specimen, only small areas of this spongy degeneration could be seen (figure 13B). In the more normal appearing areas of cortex, there were occasional small areas of infiltration by round cells and microglia and a small amount of perivascular cuffing by small round cells around some of the vessels (figure 13B and C). These changes, which were seen in the underlying white matter as well (figure 13D), were least marked in the occipital region. Astrocytic proliferation was extensive, both in the spongy areas and in areas that were better preserved.

Pathologic Summary

The right frontal lobe specimen removed three years after the onset showed inflammatory changes, with some areas of chronic spongy degeneration. The hemicorticectomy specimen removed two and one-half years later showed much more extensive and more marked spongy degeneration, with persistence of the inflammatory changes in the less severely damaged areas of the hemisphere.

Comment

In this patient, the early "flu" gives a possible explanation for etiology of the inflammatory brain disease, but its prolonged course and absence of other clinical evidence of cerebral inflammation seem to set the proc-

ess apart from the usual concept of encephalitis. Comparison of the two pathologic specimens from this patient suggested that the disease had burned itself out in some areas, leaving behind its mark in the form of spongy degeneration and diffuse astrocytic gliosis, while in other areas evidence of an active inflammatory process was still present at the time of the hemicorticectomy five years after the onset.

DISCUSSION

We believe these three patients represent various stages and degrees of the same pathologic process. We call this an encephalitis on histologic grounds, recognizing that we have no indication as to the etiology of this condition. However, localization of the lesions and their character are more consistent with a virus encephalitis[1] than with a postinfectious perivenous encephalitis or with allergic encephalitis.[2,3] It is of some interest that both case 1 and case 3 had minor systemic inflammatory episodes at the beginning of the illness. Case 2 had apparently uncomplicated measles at one year of age, four years before the onset of seizures, but there is no record of any systemic infection immediately preceding this onset.

The chronicity of the illnesses and the relatively restricted location of the lesions in these three patients would seem to set them apart from ordinary cases of encephalitis, but similar prolonged courses have been reported in cases of inclusion encephalitis,[4,5] although in other instances the course of similar or related encephalitides has been more acute.[6–8]

If these three patients were indeed all suffering from encephalitis, then it seems clear that this disease was present over a prolonged period of time, causing seizures and a slowly progressive hemiparesis without any febrile reaction or coma such as customarily accompany encephalitides. Case reports showing histologic evidence of active encephalitic lesions still present long after acute episodes of proved viral encephalitis[9–11] may give some support to the concept that the encephalitis in our three patients was of viral etiology.

Evidence of reaction in the spinal fluid (pleocytosis and elevated protein) was present in case 1 only during the second postoperative month, and was absent in the several spinal fluid examinations carried out in case 2 and case 3. More frequent spinal fluid examinations over the course of the illness in the latter two might have shown evidence of some inflammatory reaction at some time.

Comparison of the two surgical specimens from case 3 removed three years and five and one-half years after the onset suggested that this encephalitic-like process may be self limited in some patients. After gradually destroying areas of brain over a period of years, evidence of the inflammatory process apparently disappeared, leaving behind a patchy laminar necrosis and widespread diffuse gliosis. This latter picture has been a fairly frequent finding in specimens removed for the surgical treatment of focal cerebral seizures. Occasionally there has also been present in these specimens perivascular cuffing and inflammatory glial nodules. These we have attributed in the past to tissue breakdown associated with frequent seizures. These three patients, we believe, suggest that some cases of focal epilepsy for which no definite cause is evident, such as birth trauma or anoxia, head injury, or vascular occlusion, may be due to an otherwise asymptomatic focal encephalitis. If excision of the scarred area should be carried out after the active process has disappeared and healing has occurred, evidence of the inflammatory nature of the original disease might be completely or almost completely absent.

Surgery in the active phase of the disease is probably futile, except for providing a clear pathologic diagnosis. The ultimately successful outcome of cases 2 and 3, successful to date at any rate, indicates that later in the course of the disease surgical removal of the involved areas of the brain, if sufficiently complete, can stop the seizures without rekindling the inflammatory process.

Suggestions for therapy in the active phase of the disease, when it might be possible to prevent destruction of brain tissue, must await determination of etiologic factors. Serial spinal fluid examinations at weekly or monthly intervals over relatively prolonged periods of time might well be important in identifying this group of patients, so that more detailed study of possible etiologic factors might be made before the fire has burned out and only

the scarred evidence of earlier damage remains. Current speculations regarding the ability of some viruses to be dormant in the nervous system for long periods of time may be pertinent to the general problem.

SUMMARY AND CONCLUSIONS

A clinicopathologic report is made of three children suffering from a chronic illness, producing focal seizures and gradually producing severe damage to one cerebral hemisphere. The histologic appearance in each instance suggests the lesion is a chronic focal encephalitis. The etiology is undetermined, but the suggestion is made that it may be viral in nature. The possible role of similar focal encephalitic-like processes in producing certain cases of focal epilepsy is discussed.

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■ Epilepsy is a disease of the "organ of mind," that is to say, of the highest and most complex, etc., centres. The symptomatology of the paroxysm is probably a universal symptomatology, is demonstrably nearly so. It may be said that insanity is more complex than epilepsy; not so, since epileptic paroxysms are not unfrequently followed by temporary insanity. The study of epilepsy, therefore, involves the study of some cases of insanity. These insanities are what I have called after-conditions of the epileptic paroxysms. We ought, of course, to speak of epilepsies as we should do of insanities; for certainly, if two epileptics have different "warnings" of their fits, the "discharging lesion" is in a different part of the highest centres in the two cases. There are many epilepsies, and many insanities.

J. Hughlings Jackson in *Ophthalmology and Diseases of the Nervous System*, published in 1886.

Comparative effects of relaxant drugs on human skeletal muscle hyperactivity

Francis A. Vazuka, M.D.

ALTERED REFLEX RESPONSES to stretch, percussion of tendons, and skin irritations have become an integral part of the clinical examination over the years, because these reflexes are easily accessible for testing purposes without complicated instrumentations. In addition, these stimuli more nearly approach the quality and severity of afferent impulses constantly impinging upon the nervous system of the individual in his daily life. The disabling and painful spasms in patients with various neurologic diseases are triggered off, not only as a result of stretching the appropriate muscles by movement and sudden jarring, but also by cutaneous sensory stimuli which are often of only a minor nature. The alleviation of these abnormal reflex responses would result in clinical benefits to the individual.

Differences in reflex activity in humans have become amenable to recording by electromyography. The present study employs this method for detecting differences in the electrical action potentials induced by standardized myotatic, nociceptive, and stretch stimulations. A reduction in the size of the electrically recorded reflex responses is used as an indicator of drug activity.

PHARMACOLOGY

Pharmacologic properties and clinical responses produced by both Equanil and Flexin have been published on numerous occasions.[1–14] These two agents are reported to be centrally acting types of muscle relaxants which appear to exert their depressing effect on subcortical and spinal polysynaptic neural pathways. Methocarbamol (3-o-methoxyphenoxy-2-hydroxy-propyl carbamate), called Robaxin, was synthesized by Murphey in 1953 and is the monocarbamate of glyceryl guaiacolate.

In animal experimentation[15] muscle-relaxant properties of methocarbamol (Robaxin) are similar to those of Mephenesin, but of a greater potency and longer duration. Like Mephenesin the site of action of Robaxin is thus believed to be within the central nervous system where it depresses "polysynaptic" pathways at lower dosages than are required to depress "monosynaptic" pathways.

CLINICAL MATERIAL

Eleven male patients were classified according to the severity of spasticity, ankle clonus, spasms, and exaggerated myotatic reflexes, as shown in table 1. Incapacitating spasticity, clonus, and spasms were present for at least one and a half years prior to treatment. For purposes of statistical analysis the individuals were divided into two groups: one group with ankle clonus produced on dorsiflexing the foot with stirrups under graded tensions, and the second group without ankle clonus on stretching the gastrocnemius muscle on graded tensions with stirrups. One case (case 10) exhibited persistent severe "spontaneous" flexor-adductor spasms. Those cases of multiple sclerosis were used only if the spasticity was slowly progressive and incapacitating for a period of 18 months or longer.

PLAN OF STUDY AND METHODS

Clinical observations, motion picture photographic recordings, and electromyographic and myometric studies were performed on the 11 individuals with neuromuscular disorders prior to, during, and following the oral administra-

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This study was undertaken at the Veterans Administration Hospital, Richmond, Virginia.
Read before the Section on Nervous and Mental Diseases of the American Medical Association, New York City, June 6, 1957.

TABLE 1

	Case No.	Age	Duration Spasticity (years)	Spasticity	Clonus Manually Produced	Clonus with Stirrup	Spasms
Group 1	1	33	5	2+	2+	4+	2 + E x T
	2	34	2	2+	2+	2+	2 + E x T
	3	33	2	4+	4+	4+	4 + E + A
	4	25	3	4+	4+	4+	2 + E x T
	6	26	2.5	4+	4+	4+	3 + E + A
Group 2	5	20	2.5	2+	2+	0	1 + E x T
	7	48	10	4+	2+	0	0
	9	28	2	2+	2+	0	2 + E + A
	11	44	1.5	3+	2+	0	2 + E + A
	12	30	2.5	3+	2+	0	2 + E + A
Case 10		58	9	4+	2+	0	4 + FLEX.

Eleven patients were divided into two groups, depending upon the presence or absence of ankle clonus with standard tensions on a stirrup dorsiflexing the foot. Case 10 exhibited such severe flexor and adductor spasms that standardized electromyographic recordings could not be taken adequately with stirrups.

tion of Robaxin, Equanil, and Flexin. The effects on spasticity, ankle clonus, tonic and clonic extensor spasms, and the changes in functional capacity as induced by the drug administrations were noted in the subjects when each received the three drugs in series.

Appraisal of the patient's muscular tone was made by the degree of muscular resistance encountered during passive flexion and extension of the various joints, and by the ease of producing spasms on sensory stimulation. Reflex muscle spasms produced on changes in posture, shifting of the body while sitting, wheeling a chair, as well as those produced by voluntary motor acts such as shaving, eating, dressing, and walking, were recorded from observation.

Daily observations were made on ward rounds. Self-care and ambulation capabilities and complete neurologic examinations were recorded photographically on motion picture film. Cameras were placed at a standard distance from the subjects. Functional tests, such as buttoning clothing, shoelacing, walking on a level surface, and climbing up and down stairs, were standardized and performance time was measured. The cinematograhic records were taken at regular intervals while patients were on oral dosages of the drugs. In this manner each neurologic sign and symptom could later be reexamined any number of times and compared at each interval of recording for any specific alterations induced by each medication.

An evaluation of voluntary muscle power was measured by dynamometer readings at standard positions in the lower extremities. The pressure at which a 90° position of each joint was overcome indicated the standard power of the muscle group involved in flexion and extension of the great toe, the ankle, the knee, and hip joints of each leg. Strength and one-minute fatigue studies of each hand grip were performed with a clinical dynamometer. Readings were recorded at each five-second interval.

To evaluate the effect of drugs on muscles, a technic was employed of stretching the gastrocnemius muscle at graded levels of tension and electrically recording the muscle activity. Bipolar surface electrodes were placed at standardized positions over the belly of the peroneal, gastrocnemius, quadriceps, and hamstring muscles of each lower extremity. The leads were connected through a Grass machine differential amplifier to the multichannel inkwriting apparatus. Immobilization of the insulated electrodes to the skin prevented artifacts from appearing in the recording, even with severe clonus.

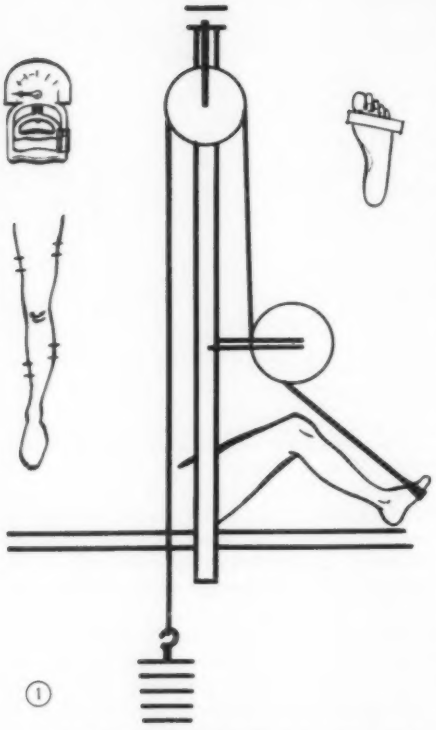

FIG. 1. Method of dorsiflexing the feet under graded levels of tension. Adding successive weights dorsiflexed the foot to effect graded levels of tension in the gastrocnemius. The rope tugged parallel to the longitudinal axis of the shin. Bipolar electrodes were placed on the peroneal, gastrocnemius, quadriceps, and hamstring muscles in both legs. Immobilizing the insulated electrodes to the skin prevented artifacts from appearing in the records, even with severe clonus. Stirrup placement was standardized, with the edge of the strap along the skin fold at the base of the big toe and the little toe. Hand grip fatigue studies were performed concurrently.

Stirrup placement across the sole of the foot was standardized, with the distal edge localized to the level of the skin fold at the base of the little and of the great toes, as illustrated in figure 1. The rope attached to the stirrup dorsiflexed the foot and tugged parallel to the longitudinal axis of the shin. It was then led across two pulleys so that weights could be attached to the other end of the rope to effect various grades of tension. Adding successive weights thus produced varying tensions on the ball of the foot and stretched the gastrocnemius muscle at graded levels. Testing while the knees were extended produced more uniform records than when the knees were slightly flexed.

The patellar and Achilles tendon were stimulated by a standard blow of a reflex hammer. Electrical potentials from all eight muscles (peroneal, gastrocnimius, quadriceps, and hamstrings bilaterally) were recorded simultaneously. Action potentials from the responding gastrocnemius under graded tensions serve as simple and reliable indicators of reflex activity provoked by the reflex receptors. Alterations in severity of ankle clonus and in severity of response to sensory stimuli are readily apparent and amenable to statistical analysis.

MEDICATION

In the present clinical evaluation, Robaxin was administered orally for one month in dosages of 5 gm. per day in four divided doses. After the reflex activity and the spasticity returned to the premedication levels, each patient was then placed on Equanil for one month in oral doses of 400 mg. either three or four times daily. Finally the same individuals were administered Flexin for one month in oral doses of 500 mg. either three or four times a day.

RESULTS

The results of electromyographic recordings derived from both the right and the left gastrocnemius in the patients in group 1 were pooled for purposes of statistical analysis. The test results obtained during treatment with each of the three medications were compared with the premedication data. The means and variances of the readings were calculated and differences between each drug therapy and the control period were analyzed statistically at a confidence value of 0.05.

The myographic recordings (figure 2) revealed that significant changes occurred both in the force of the stimulus evoking clonus and in the amplitude of the clonus. The weight range (figure 3) on the stirrup producing ankle clonus prior to medication varied from 5.9 to 16 lb., with a mean weight of 10.7 lb. Equanil (400 mg. three or four times daily) produced the best response of the three drugs, with significant reductions in the low, the

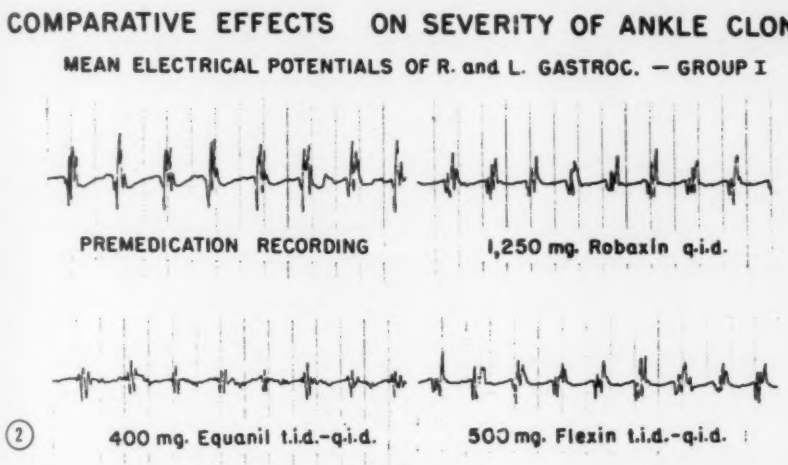
COMPARATIVE EFFECTS ON SEVERITY OF ANKLE CLONUS
MEAN ELECTRICAL POTENTIALS OF R. and L. GASTROC. — GROUP I
PREMEDICATION RECORDING
1,250 mg. Robaxin q.i.d.
400 mg. Equanil t.i.d.-q.i.d.
500 mg. Flexin t.i.d.-q.i.d.
2

FIG. 2. Recordings of the mean amplitude of ankle clonus as measured by the electrical potential of the gastrocnemius at the control level and as induced by the three drugs is illustrated. Reduction of the mean amplitude of the clonus was greatest with Equanil.

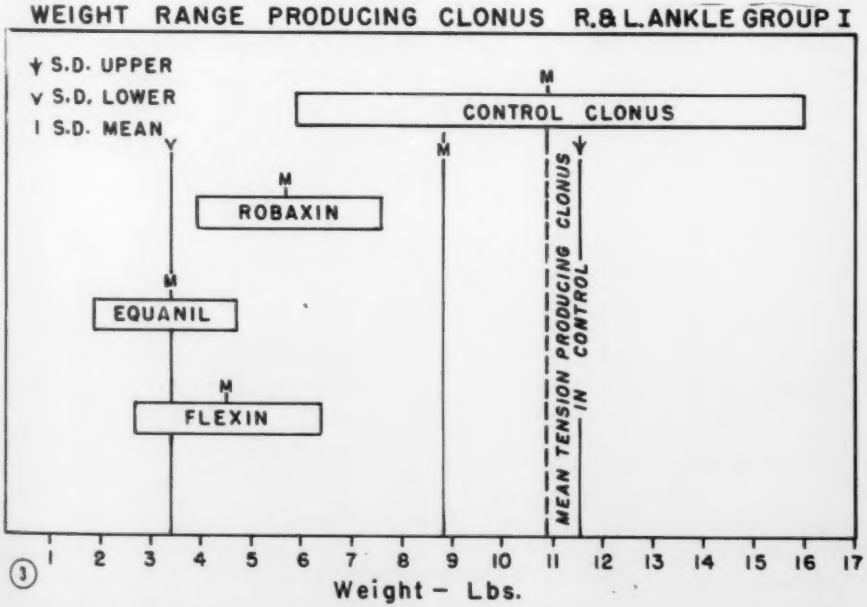
WEIGHT RANGE PRODUCING CLONUS R.& L. ANKLE GROUP I
+ S.D. UPPER
v S.D. LOWER
I S.D. MEAN
CONTROL CLONUS
ROBAXIN
EQUANIL
FLEXIN
MEAN TENSION PRODUCING CLONUS IN CONTROL
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Weight — Lbs.
3

FIG. 3. Equanil effects the greatest reduction in the weight range that produces clonus in the right and left ankle of group 1.

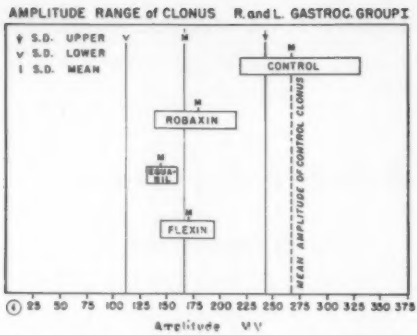
AMPLITUDE RANGE of CLONUS R. and L. GASTROC. GROUP I
+ S.D. UPPER
v S.D. LOWER
I S.D. MEAN
CONTROL
ROBAXIN
EQUA-NIL
FLEXIN
MEAN AMPLITUDE OF CONTROL CLONUS
0 25 50 75 100 125 150 175 200 225 250 275 300 325 350 375
Amplitude MV

FIG. 4. The greatest reduction of the mean amplitude of clonus occurred with Equanil. Robaxin and Flexin decreased the amplitude of the clonus to similar levels.

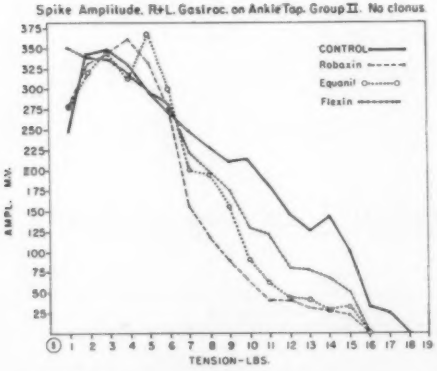
Spike Amplitude. R+L. Gastroc. on Ankle Tap. Group II. No clonus
CONTROL
Robaxin
Equanil
Flexin
AMPL. MV.
375 350 325 300 275 250 225 200 175 150 125 100 75 50 25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
TENSION-LBS.

FIG. 5. Robaxin produced the greatest reduction of the electrical spike potential from 7 to 11 pounds of tension in the nonclonus group.

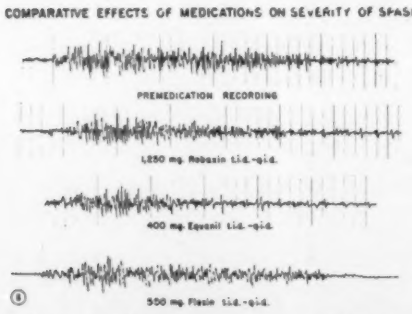

FIG. 6. Records illustrating that the severity and duration of spasticity on passive stretching are reduced to a greater extent by Equanil than by the other two drugs at the dosage regimen described.

mean, and the upper weights. Flexin (500 mg. three or four times daily) also produced significant reductions in the three tension variances, but the response was not as great as that appearing with Equanil. Robaxin (1,250 mg. four times daily) brought about significant reductions in the mean and upper weights, but did not bring about significant reductions in the lower tension that produces clonus.

The amplitude (figure 4) of the electrically recorded clonus in the control study varied from 219 to 331 microvolts, with a mean amplitude of 268 microvolts. Significant reductions in the amplitude of the mean electrical potential from the gastrocnemius muscles occurred only with Equanil. However, significant deviations from the control trials occurred in the upper limit of the amplitude of the clonus with all three drugs. No significant reduction occurred in the lower limit of the amplitude with any drug tested.

The mean amplitude of the electrical spike recorded from the right and the left gastrocnemius in the nonclonus group evoked by percussing the Achilles tendon with a reflex hammer is illustrated in figure 5. The gastrocnemius muscle in each case was tested under graded levels of tension. Significant reduction in the amplitude of the spike potential occurred from 10 through 14 and at 16 lb. of weight with Robaxin and with Equanil. Robaxin, however, affected a greater depression in the spike potential than did Equanil. Flexin produced significant reductions in the potential only at 16 lb. of weight. No significant reduction in the amplitude of the spike potential in the gastrocnemius occurred in the nonclonus group with any medication tested when the muscle was under graded tensions with the 1 lb. through the 9 lb. weights.

The variations in clonus, spasms, and spasticity as induced by drug administration are listed in table 2. The greatest reduction in the mean weight that initiates clonus occurred with Equanil. A more pronounced reduction occurred with Flexin than with Robaxin. Only Equanil produced significant reduction in the mean amplitude of the ankle clonus.

A decrease in the severity and duration (table 2) of spasms elicited by stroking the feet indicates another aspect in the depression of hyperreactivity induced by these drugs. The

TABLE 2

VARIATIONS IN CLONUS, SPASMS, AND SPASTICITY INDUCED BY MEDICATIONS

	Control	*Robaxin*	*Equanil*	*Flexin*
Mean weight producing ankle clonus (LBS)	10.9	5.7	3.3	4.5
Mean amplitude of ankle clonus (M.V.)	267	180	148	172
Clonus on resting legs on balls of feet (number of patients)	9	5	4	8
Spasms on stroking feet				
Severity	25.1	9.6	14.0	17.9
Duration (seconds)	3.2	1.8	2.4	2.6
Spasticity on passive stretch				
Severity	33	20	16	22
Duration (seconds)	2.5	2.0	1.5	2.2
Clinical clonus (with daily routines)	28	17	10	24
Clinical spasms (with daily routines)	24	9	14	23
Clinical spasticity (with daily routines)	34	23	20	28

data record the severity and duration of the electrical potentials induced in the leg muscles as a withdrawal response to a cutaneous sensory stimulus applied to the sole of the foot. Robaxin affected the greatest depression in response to the cutaneous stimulus. Equanil and Flexin produced nearly equal reduction in responses.

Spasticity to passive stretching (table 2) was reduced to a greater extent by Equanil (figure 6). On passive stretching Robaxin produced some alleviation and Flexin the least depression of spasticity.

To evaluate the over-all clinical effectiveness of the drugs on ankle clonus, spasms, and spasticity, each of these three modalities of skeletal muscle hyperactivity was assigned a degree of reactivity rated from 0 to 4+. The highest figure was assigned to each modality in the 11 individuals which produced a maximal response with a minimal stimulus. A 4+ value for spasms was assigned to those who responded with a spasm to blowing on the skin of the legs. The greater the stimulus required to produce a spasm, the less the value assigned to that spasm. Production of spasms was also noted on other cutaneous stimulations, such as jarring the bed, moving the arms, shifting the weight in bed, sitting, attempting to dress, shifting the body from the bed to the chair, propelling a wheel chair, and standing. Similar and other appropriate types of observations were recorded for clonus and for spasticity and levels of hyperreactivity were assigned.

The degree of the clonus, spasms, and spasticity occurring during daily hospital routines was recorded during treatment with each medication. These values were totaled in each individual at the end of the drug therapy, as noted in table 2.

Ankle clonus was depressed greatest by Equanil. Robaxin brought about the greater depression of spasms, except during one or two day periods of emotional disturbances. The spasms would then return, but not to the premedication levels. No drug exhibited any marked reduction in spasticity, but 400 mg. of Equanil three or four times daily produced a depression slightly greater than 1,250 mg. of Robaxin four times daily.

The relief or reduction in the severity of spasms sufficient to allow performance of daily routine, self-care activities by patients, and the attendant reduction in the need for aides were the greatest benefits derived from these muscle relaxants. An improvement in the patient's ability to perform essential daily minimal self-care needs was apparent by the greater number of patients who were able to comb their hair, wash their faces, brush their teeth, shift onto a commode, stand and shower by

themselves, and dress themselves. Less frequent incontinence occurred due to a reduction of the severe spasms.

Ambulation was improved so that spastic and tonic gaits became "looser" and more natural with Robaxin and with Equanil, which also gave nearly parallel improvement in self-care abilities. One wheelchair patient had such relief of spasms that he was able to walk with a cane, even up and down stairs, while on Robaxin and Equanil. A bed patient had sufficient relief of spasms while on Robaxin and Equanil that he became a wheelchair patient. Two wheelchair patients were able to ambulate with crutches while on these same two medications. Two bed patients were more easily cared for because of reduction of spasms which was brought about most effectively, but irregularly on a day to day basis, by Robaxin.

SIDE EFFECTS

Robaxin in dosages of 5 gm. per day produced subjective tiredness, fatigability, exhaustion, and weakness in six individuals. These complaints were persistent and were not relieved by rest or sleep. Muscle strength studies in the lower extremities and one-minute hand grip studies did not reveal any muscle weakness or any muscle fatigue for the period tested. However, performance of such daily activities as walking and climbing stairs revealed that, in the total functional capacity of the muscles, fatigue and performance were slower. It is difficult to assess to what extent relief of spasticity contributed to these symptoms.

Nervousness, anxiety, inward tension, shakiness, and jittery nerves were symptoms expressed by eight of the 11 individuals at varying intervals while on Robaxin. Anxiety and tension appeared to be more easily initiated by minor situational personal or home problems. During these episodes of anxiety, spasms again returned and were triggered off more easily while on Robaxin, but not to the premedication levels. The lack of tranquilizing effects by this agent on the psychic component of spasticity and spasms may account for the varying results on a day to day basis. Four patients on Robaxin offered the information that their muscles felt loose, relaxed, no longer tense, and yet they felt inward tension, shakiness, and nervousness throughout the period of medication. They requested some agent to calm their nerves. It may well be that a central nervous system component contributes to the increased propensity for anxiety, fatigue, and exhaustion with this medication.

Equanil in dosages of 400 mg. three or four times daily produced fewer side effects. Three individuals who received 400 mg. of the medication four times a day experienced drowsiness to the point of nodding off to sleep while sitting. With reduction of the dose to 400 mg. three times a day, alertness and calmness returned. One patient complained of persistent weakness while on 400 mg. three times a day. Muscle strength and myometric fatigue studies revealed no increased weakness or increased fatigability of the muscles on one-minute studies.

Impotence occurred in the same three individuals that experienced this symptom with Robaxin. With Equanil, however, impotence paralleled the reduction of spasticity.

No patient complained of anxiety while on Equanil, and the daily fluctuations of spasms were markedly less pronounced than with Robaxin or Flexin. Rather, patients felt calm and emotionally relaxed. Two individuals with more severe spasms than when taking another drug stated they preferred Equanil because they were emotionally calm and were willing to ignore the muscle symptoms.

Gastrointestinal symptoms occurred as side effects with Flexin. One individual developed a rash and nausea and vomiting when Flexin was increased to 1,000 mg. four times a day, but these disappeared on reducing the dose to 500 mg. four times a day. Another patient developed a rash and nausea when 500 mg. of Flexin was given three times daily. Medication was then changed to engestic coated Flexin 500 mg. three times a day; the nausea disappeared in two days and the rash disappeared in two weeks. No alterations occurred in the white blood count. Nausea and vomiting occurred in two other individuals when the medication was increased to 1,000 mg. four times a day but quickly disappeared on reducing the dose to 500 mg. four times a day.

Tiredness and weakness were produced in three patients while on Flexin 500 mg. four times a day. No loss of strength or fatigability occurred on myometric studies. Nervousness

occurred in four individuals, with concurrent increase in clonus, spasm, and spasticity. Impotence did not develop in any patients while on Flexin.

DISCUSSION

Robaxin, Equanil, and Flexin exert moderate blocking action on interneurons in humans, this action being demonstrated by the initial disappearance of crossed extensor, crossed adductor, and crossed Babinski reflexes in humans.[16] Different responses to these three agents may be explained by the variances in activity and potency of the drugs, by differences in the severity of the symptoms, and by the state of central excitability which is influenced by the emotional state of the individual. No practical clinical result has been observed with any oral medication in relieving severe spasticity and severe spontaneous flexor spasms. If spasms are mild, the drugs may effect a relief or reduction of the symptoms. Reflex spasms and clonus showed considerable fluctuations in severity on different days, depending on the variations in the state of central excitability. This was especially prominent with Robaxin and with Flexin. Correlation between an increase in excitability of hyperactive muscles and an increase in nervousness, anxiety, and tension was apparent in patients receiving both Flexin and Robaxin. However, great fluctuations in symptoms on a day to day basis were not present with Equanil.

Tranquilizing properties of Equanil tend to produce more stable conditions of emotional tension during the formal test procedures and thus tend to show more uniform results. Patients receiving Robaxin and Flexin, on the other hand, were tested under conditions of widely fluctuating levels of emotional and central nervous system excitability. This may account for part of the less favorable test results in individuals who were maintained on these two drugs.

The use of electromyography as an adjunct to clinical observation for evaluating the effect of muscle relaxants is a useful method applicable to humans, provided that the conditions under which the procedures are performed are standardized. The extent to which the electromyographic record is modified by various drugs in the test situation has been found to correlate well with the degree of clinical relaxation induced in the muscles.

The major benefit derived by the 11 patients was a partial alleviation of muscle hyperreactivity, which in turn allowed for greater self-care capabilities and easier ambulatory capabilities. Urinary frequency was lessened. Wheelchair patients could sit more comfortably and manipulate the chair without aid. Movements no longer threw their extremities into severe clonic extensor spasms.

Ambulatory and bed patients complained of a great deal of weakness while on Robaxin. This degree of weakness was not proportional to the amount of muscle relaxation attained. Therapy was not abandoned when a patient presented this complaint, because periodic myometric studies did not reveal any weakness or increased fatigability over a one-minute period of goniometric studies.

Great advantages did accrue with combinations of Equanil and Robaxin and with combinations of Equanil and Flexin. The combination of Equanil and Flexin appeared to be more potent in relieving spasticity and spasms and in suppressing anxiety than when Equanil and Robaxin were used. However, sufficient data is not available for an adequate evaluation of drug combinations.

It should be stressed that anxiety alone did increase spasms, spasticity, and clonus. Spasms were made considerably worse by smoking, even though patients felt more relaxed emotionally. All symptoms of muscle hyperreactivity were aggravated the day following alcoholic intake, even at nonintoxicating levels.

None of the three drugs produced any alterations in the blood pressure and pulse, nor was there any anemia, leukopenia, jaundice, or disturbed kidney function.

SUMMARY

Clinical observations, motion picture photographic recordings, and electromyographic and myometric studies were performed on 11 individuals with neuromuscular disorders prior to, during, and following the oral administration of 1,250 mg. of Robaxin given four times a day, 500 mg. of Equanil given three or four times a day, and 500 mg. Flexin given three or four times a day. Alterations were noted

on spasticity, ankle clonus, clonic extensor spasms, flexor spasms, and functional capacity as manifested by self-care and ambulation abilities. The variations were recorded when each subject received the three drugs in series. Each modality of muscle hyperactivity was not depressed to parallel levels. The present study indicates that Equanil in the dosage noted above is more effective than Flexin and Robaxin as a muscle relaxant in the human. The above mentioned dosage of Robaxin has been found to be more effective in relieving muscle spasticity than Flexin.

The author is indebted to Miss Nancy Walke and Mr. Henry Kelley for their assistance in performing the electromyographic recording, and to Mr. Junis Billups and Mr. William T. Kidd for their assistance in the photography. He also wishes to express grateful appreciation to Dr. James Cottrell, the manager, and to the members of the research committee of the Veterans Administration Hospital, Richmond, Virginia for their advice and encouragement throughout this study.

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■ I shall now speak of the usually assigned causes of epilepsy; and first of those which predispose to the disease. With regard to *predisposition* to idiopathic epilepsy, we have no clear and distinct knowledge. We cannot ascertain its nature, or even its existence in many cases, or whether or not, it be necessary to the formation of the complaint. Some pathologists are of opinion, that it is not necessary, and that epilepsy may be produced, and in some cases has been produced, by a new and strong impression in a perfectly well organized brain and nervous system, and independently of predisposition. Be this as it may, I am inclined to believe, nay, I think it is evident, that a certain constitution of brain and nervous system exists in particular persons, which renders them especially liable to this disorder; that there is a much greater sensibility, irritability, or what Dr. Cullen calls mobility of brain and nerves, in some persons than in others, which constitutes predisposition to epilepsy.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Spinal fluid protein in tumors of the sellar region

Louis Bakay, M.D.

THE SPINAL FLUID protein content in patients with pituitary adenomas or other tumors of the sella turcica represents a problem of clinical as well as theoretical interest. In the past, it was not known whether there is a relationship between the size of an adenoma and the amount of cerebrospinal fluid protein and whether conclusions could be drawn from the protein content regarding the rate of growth or recurrence of such a tumor.

From a theoretical point of view, pituitary adenomas are unique among intracranial tumors because of their relationship to structures of the cranial cavity. Every pituitary adenoma is extracranial in its early stage as far as the cerebrospinal fluid is concerned. During this early phase the adenoma is situated entirely in the sella. During the second stage of its growth, it reaches over the level of the diaphragma sellae and becomes a truly intracranial tumor. At this time, changes in the composition of the cerebrospinal fluid can be expected.

MATERIAL AND METHOD

Fifty patients with tumors of the sellar region have been studied. Of these, 28 were pituitary adenomas (26 chromophobe, two acidophil), ten craniopharyngiomas, and 12 others, including suprasellar meningiomas, metastases to the pituitary gland, chordomas, and gliomas of the optic nerves.

The location, as well as the size, of the neoplasms was determined radiologically after outlining them with air.[1] Direct measurements were made in two planes, and the results were corrected to avoid the linear enlargement (9 to 12 per cent) by roentgenograms. This method gave better information about the relationship of the tumors to the cerebrospinal fluid spaces than surgical notes. Large suprasellar growths are rarely exposed completely during the operative procedure, and even in smaller lesions the size is determined only by estimation. An error of a half centimeter in estimating the diameter of a round tumor is seemingly quite acceptable, and yet this leads to an almost 50 per cent error in the estimation of the volume of a tumor in the 2.5 to 3.0 cm. diameter range.

In several instances the adenoma was visualized repeatedly by air studies, and the cerebrospinal fluid findings could be correlated with the actual situation prevalent at the time of fluid sampling. Of the 50 cases, 40 (80 per cent) were directly observed at operation or autopsy, or both.

The protein determination was performed in spinal fluid obtained by routine lumbar puncture. Only two of these patients had increased intracranial pressure. When the spinal fluid was obtained in the course of pneumoencephalography, the first 3 cc. were collected for protein determination to avoid dilution by cisternal fluid and to maintain uniformity in sampling.

The spinal fluid was mixed with 5 per cent sulphosalicylic acid, and the resulting turbidity was determined by photocolorimetry and calculated to a protein standard. The upper limit of normal with this method is 45 mg. per cent for lumbar fluid protein, but it was extended in this study to 50 mg. per cent. Values between 50 and 55 mg. per cent were considered "borderline."

RESULTS

Of the 28 pituitary adenomas (table 1), six (cases 1 to 6) were entirely intrasellar, although the sella which they occupied was greatly expanded. Only one of this group had a mildly increased spinal fluid protein (57 mg. per cent), and that only at the time of pituitary apoplexy; very shortly afterward the

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TABLE 1

PITUITARY ADENOMAS*

Case	Sex	Age	Size and Location	CSF Protein in mg. %
1	F	55	Entirely intrasellar	27 to 37
2	M	25	Confined to the greatly enlarged sella	39
3	M	49	Large, entirely intrasellar adenoma; acute pituitary apoplexy	57, later 22
4	F	43	Large, but intrasellar	46
5	F	39	Does not extend beyond enlarged sella	39
6	F	54	Intrasellar	38
7	F	47	Small adenoma with slight narrow protrusion upward	48
8	F	47	Slight suprasellar extension without elevation of the floor of the third ventricle	41 to 50
9	F	37	Largely confined to big sella; some suprasellar extension	33
10	M	60	Very large adenoma, reaching the floor of lateral ventricles	76
11	F	52	Extends 2 cm. above sella and also to the right	168
12	F	62	Adenoma extends 3 cm. above operculum sellae	104
13	F	52	Huge adenoma, containing 18 gm. of tissue	74
14	M	43	Suprasellar extension from a greatly ballooned sella	108
15	F	58	Adenoma reaches 3.0 cm. above the entrance to the sella	72 to 90
16	M	39	Extends 2 cm. above the sella	72
17	F	49	2 cm. extension in superior and posterior direction	30 to 34
18	M	50	2 cm. extension upward	85
19	F	55	Large sella with adenoma extending 2 cm. higher up	33
20	F	67	Suprasellar extension: 3.0 cm.	190 to 200
21	F	73	Adenoma is 4 cm. in diameter, completely deforming third ventricle	81
22	F	22	Large suprasellar extension, elevating anterior horns	350 to 500
23	F	44	Adenoma 4.0 cm. in diameter	60
24	F	43	2.5 cm. suprasellar extension	65 to 90
25	F	65	Adenoma extends at least 2 cm. above the operculum	84
26	F	36	Suprasellar extension: 1.5 cm.	63
27	F	52	Very large adenoma, extending over 4 cm. above the sella into the frontal horns and third ventricle	85
28	M	20	Adenoma reaches 1 cm. above the enlarged sella	80

*1 to 26 were chromophobe adenomas, 27 and 28 acidophil.

protein diminished to 22 mg. per cent. An additional three patients (cases 7 to 9) had adenomas extending slightly above the level of the entrance to the sella. They also had normal spinal fluid protein.

Nineteen patients had large adenomas extending from the sella to a considerable distance. Only two (10.5 per cent) of this group had normal protein; the rest showed values from 60 to 500 mg. per cent, with an average of 117 mg. per cent.

Any impairment of the visual fields in itself indicates a certain expansion of a pituitary adenoma beyond the anatomic confines of the sella turcica, and this symptom was present even in those adenomas which were described as intrasellar. However, in these cases the expansion was limited to a slight upward curving of the adenoma that did not break through the diaphragma sellae. Further cranial extension at least 0.5 cm. above the level of the sellar entrance represents true intrusion into the chiasmatic or interpeduncular cisterns. A suprasellar extension of 1 cm. reaches the anterior-inferior tip of the third ventricle, and an extension of 2 cm. causes a definite defect in the ventricle, particularly when it proceeds in a superior-posterior direction. Extension of

TABLE 2

CRANIOPHARYNGIOMAS

Case	Sex	Age	Size and Location	CSF Protein in mg. %
29	M	14	Entirely intrasellar (enlarged sella)	31
30	F	67	Small intrasellar cyst, compressing chiasm from below	37
31	M	46	Large suprasellar cyst (3 cm. diameter), fills almost entire third ventricle	108
32	M	29	Large cystic tumor, occupying anterior third ventricle	76
33	F	59	Adamantinomatous type, elevates third ventricle. Cyst contains 10 cc. of fluid	22 to 30
34	M	42	Tumor in anterior third ventricle, diameter: 3 cm.	56
35	M	63	Suprasellar cyst, 3.5 cm. in diameter	80
36	M	17	Suprasellar cyst, 4 cm. in diameter, occupying third ventricle and causing obstructive hydrocephalus	52
37	F	44	Suprasellar tumor, bulging into third ventricle	43
38	M	66	Large adamantinomatous tumor; fills third ventricle. Obstructive hydrocephalus	116

In cases 36 and 38 the air was introduced by ventricular puncture.

TABLE 3

MISCELLANEOUS TUMORS

Case	Sex	Age	Size and Location	CSF Protein in mg. %
39	F	67	Anterior clinoid meningioma, 2.5 cm. in diameter, quite anteriorly located	52
40	F	44	Suprasellar meningioma; diameter: 2 cm.	100
41	F	51	Meningioma of medial sphenoid wing, involving sella	80, later 224
42	F	63	Chordoma, destroying clivus and sella, protruding into nasopharynx	40
43	M	63	Chordoma, destroying dorsum sellae	44, later 64
44	F	4	Glioma of left optic nerve	42, later 132
45	M	3	Glioma of right optic nerve	124
46	F	64	Carcinoma of sphenoid sinus with invasion of the sella	94
47	M	58	Pituitary metastasis from thyroid carcinoma with extension into the interpeduncular cistern	85, later 124
48	M	62	Pituitary metastasis from adrenal carcinoma, elevating floor of third ventricle	134
49	F	15	Malignant teratoma, arising from sella and extending into the third and lateral ventricles	600
50	M	29	Unclassified malignant tumor, destroying sella and extending 2 cm. upward	92

3 cm. carries the adenoma well up in the anterior half of the third ventricle, and another one-half to one centimeter approaches the interventricular foramen. The foramen is rarely obstructed because of the posterior displacement of the third ventricle. The floor of the anterior horns of the lateral ventricles can be elevated or indented by very large adenomas. This sign indicates that the tumor extends at least 3.5 cm. above the sella.

These data show that the great majority of pituitary adenomas that extend beyond the boundaries of the sella turcica increases the protein content of the cerebrospinal fluid. There are exceptions to this rule, but the relationship between size and location of the tu-

mor and the increase in spinal fluid protein is rather direct.

The spinal fluid protein in other tumors of the sellar region was more variable and less predictable. Two of the ten craniopharyngiomas (table 2) were intrasellar and were thought to be adenomas until the time of operation. The spinal fluid protein was normal. The remaining eight tumors were truly suprasellar cystic structures in close relation to the third ventricle. Yet, two of these eight patients had entirely normal protein and another two slightly (52 to 56 mg. per cent) increased protein. Only one had increased intracranial pressure and obstruction at the level of the third ventricle, a condition that would explain poor communication with the spinal fluid.

In the miscellaneous group (table 3) normal or borderline protein was found in three out of 12 cases (25 per cent). One was an anterior clinoid meningioma growing subfrontally, another a chordoma destroying the base and penetrating the nasopharynx, and the third an optic nerve glioma in its early stage of development.

Since these data were obtained from lumbar subarachnoid fluid, one cannot draw definite conclusions as to the exact place where the additional protein was added to the cerebrospinal fluid. However, it is obvious that extrasellar portions of the neoplasms, particularly of pituitary adenomas, are in close contact with the fluid of the chiasmatic and interpeduncular cisterns and that this close spatial relationship is the cause of increased protein content. When the growths reach large size, they come in close contact with the third ventricle, and the fluid of this compartment is also likely to contain abnormally large amounts of protein. In one of our patients (case 11) who had a large chromophobe adenoma, the lumbar fluid contained 168 mg. per cent of protein, while the fluid from the left lateral ventricle contained 184 mg. per cent, and that from the right lateral ventricle 258 mg. per cent.

Repeated protein determinations over a period of time might give a clue as to the rate of growth of the tumor. In a metastatic tumor of the pituitary (case 47), the lumbar protein increased from 85 to 124 mg. per cent within one month. A similar, although usually slower, increase can follow the expansion of more benign tumors. In one patient (case 4) radiographically demonstrated extension of a chromophobe adenoma beyond the sella increased the protein from an original 46 to 60 mg. per cent. Similar observation was made on an expanding craniopharyngioma (case 32), from 54 to 76 mg. per cent within one year. Gradual changes in protein are impressive when correlated with the air studies. In case 24 gradual, but relatively fast and uncontrollable growth of a chromophobe adenoma was followed visually over a period of two years. Hand in hand with this observation, the spinal fluid protein increased from 65 to 90 mg. per cent and finally to 174 mg. per cent. An optic nerve glioma (case 44) increased the protein from 42 to 132 mg. per cent as soon as it recurred and encroached on the chiasm and on the hypothalamus.

Equally interesting is the decrease in the abnormally high protein content when it follows successful treatment of the tumor. In one of the meningiomas (case 41) protein increased from the initial 80 to 224 mg. per cent as the tumor increased in size, but one year following a subtotal removal it was found to be reduced to 73 mg. per cent. Removal of another meningioma (case 40) decreased the protein from 100 to 35 mg. per cent. Partial removal of a chromophobe adenoma followed by energetic radiation therapy reduced the protein content from 90 to 54 mg. per cent for a period of five years (case 15). This increased again to 66 mg. per cent and later to 72 mg. per cent as soon as further expansion occurred. Radiation therapy alone can produce such decrease in protein. This was particularly impressive in a metastasis to the pituitary, where marked clinical improvement coincided with a reduction of protein from 134 to 59 mg. per cent (case 48).

DISCUSSION

There are only a few reports in the literature about the protein content of the cerebrospinal fluid in pituitary adenomas or other tumors of the vicinity of the sella turcica. The largest series (17 adenomas and six craniopharyngiomas) was published by Scheller,[2] who came to the conclusion that the cerebrospinal fluid findings are quite variable in these patients. About one-third of the adenomas

showed increased protein, but no attempt was made to correlate this finding with pertinent clinical data. Nothing was known about the exact location and extent of the tumors, since they were not visualized either by radiography or by surgical or anatomic exposure. Bannwarth,[3] in his otherwise very stimulating paper on the relationship between brain tumors and cerebrospinal fluid protein, briefly commented on the markedly increased protein content in four craniopharyngiomas. These were very large and filled most of the third ventricle.

The data presented here differ from previous reports, not only in the number of cases but in other factors as well. The protein determination was much more accurate than in the German publications of the 1930's. In addition, these laboratory findings were correlated with the clinical course of the patients, as well as with the actual size and location of the tumor at the time when the lumbar puncture was performed. Frequently, it was repeated over prolonged periods of time. In the overwhelming majority, the diagnosis was verified by surgical biopsy and, in those patients who died, by autopsy.

There seems to be no doubt that, from a spatial point of view, the close relationship between tumors arising from the sella turcica and the fluid in the surrounding basal cisterns is responsible for the increased protein content. However, the physiologic mechanism behind this phenomenon is not well known. As a matter of fact, any explanation of changes in cerebrospinal fluid protein is hypothetical, due to our imperfect knowledge of the source of this protein.

Experiments with the use of labeled radioactive albumin led to the conclusion that plasma is the immediate source of cerebrospinal fluid albumin.[4,5] Electrophoretic studies also indicate that a large amount of the proteins of the cerebrospinal fluid derive from proteins of the plasma. The various protein fractions are identical with those in the plasma, except for a rapidly migrating albumin, called component X, or prefraction, which occurs in normal cerebrospinal fluid, where it constitutes from 3 to 13 per cent of the total proteins.[6–8] No differences in the concentrations of component X were observed in spinal fluids from patients with brain tumor.[8] This fraction may represent a protein which arrives in the cerebrospinal fluid by a break-down process within the central nervous system. However, the existence of this fraction is still disputed. Comparison of serum and cerebrospinal fluid gamma globulin determined by an immunochemical method in the same individuals strongly suggests that the gamma globulin of cerebrospinal fluid is derived in part from the blood and in part from tissues of the nervous system.[9]

These findings cannot be extended without reservation to the increased protein content of the spinal fluid under pathological conditions. In tumors of the brain, the increased protein content can be caused by an increased vascular permeability, which is usually local. The tumor vessels themselves lead to capillary exudation. In addition, the tumor can cause local obstruction of venous blood flow, which results in increased filtration of material through the capillaries into the cerebrospinal fluid. Slowing down the cerebrospinal fluid circulation may be another cause of increase in proteins, because the slowly moving fluid cannot remove proteins adequately. The isotopic studies of Sweet and associates[5] showed that defective absorption, along with no excessive entry of protein, can be responsible for the accumulation of cerebrospinal fluid protein. In addition, proteins are undoubtedly also supplied by metabolic break-down of tumor tissue. The importance of this latter is not known. Electrophoretic studies by Scheid and Scheid[10] showed that the increased protein content of the spinal fluid in meningitis and in brain tumors is composed of the same proteins that are present in the blood plasma. Similar results were obtained by Steger[7] in the content of cystic tumors.

SUMMARY

The protein content of the spinal fluid was determined in 50 patients with tumors of the sellar region. The findings were correlated with the type, size, and exact location of the neoplasm, as verified by pneumoencephalography, operation, or postmortem examination.

The protein content was normal in pituitary adenomas which were confined to the sella turcica. Ninety per cent of adenomas with extrasellar extension had increased spinal fluid protein.

The relationship between craniopharyngiomas, as well as other nonadenomatous tumors, and the spinal protein content was less clear, although increased protein was found in the majority of patients.

Further growth or recurrence of sellar tumors was frequently heralded by increase in spinal fluid protein. Arrest or significant removal of a neoplasm, either by surgery or radiation therapy, resulted in a reduction of protein.

The possible causes and physiologic mechanism of these spinal fluid changes are discussed.

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■ Atrophy of the spinal cord, like atrophy of the brain, is one of the changes which must be looked upon as natural to old age. In elderly persons, indeed, the cord becomes shorter and narrower and firmer, the spinal fluid increases in quantity, so as to fill the space left vacant by the shrunken cord, and the spinal nerves are sensibly wasted at both their roots. All this has been abundantly proved by Chaussard, Ollivier, and others. Atrophy, more or less general, is also associated with many forms of paralysis in which the cord has been long left in a state of comparative functional inactivity; and local atrophy is one of the consequences of tumour, displaced vertebrae, or anything which exercises pressure upon the cord. Of partial forms of atrophy resulting from disease, the only one about which there is any certain knowledge is that which is associated with the disease called locomotor ataxy — namely, atrophy of the posterior columns.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves,* published in 1871.

Alcoholic gasserian injection for relief of tic douloureux

Preliminary report of a modification of Penman's method

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NEUROSURGEONS have been reluctant to inject alcohol into the gasserian ganglion or root, because of the risk to ophthalmic fibers and to other cranial nerves.[1–5] However, in the hands of some experts[6,7] the procedure seemed satisfactory. A few years ago Penman[8,9] described a method of injecting the posterior root of the gasserian ganglion under radiologic control. Preliminary radiographic study determined the entry point of the needle and the required relationship of the needle to the individual patient's skull. After insertion of the needle, further radiographic study indicated the position of the needle in the base of the skull and permitted accurate adjustment of its depth. The effect of injecting a tiny amount (0.03 cc.) of procaine was judged by careful sensory testing. Thus, the exact relation of the needle to the posterior root was deduced before any significant risk was taken. Only then were minute amounts (each 0.05 cc.) of absolute alcohol injected. Penman[4] produced immediate relief of tic douloureux in 97 per cent of his first 100 cases. Unfortunately, 82 per cent of these patients suffered corneal anesthesia and 15 per cent required tarsorrhaphy because of keratitis; in only one case, however, was there persistent corneal opacity.

Three years ago, we were impressed by the precision which Penman's method offered in placing the needle and also by the minute amounts of alcohol injected at one time. We considered that involvement of ophthalmic fibers (in root, ganglion, and division) had been due in some cases to their being highest in Meckel's cavity in the upright position and with the large amounts of alcohol then employed. Thus, they were exposed to any alcohol (S.G. 0.775) escaping into and rising in the cerebrospinal fluid (S.G. 1.003) of the cavity. Therefore, we minimized this risk by modifying Penman's method so that the patient was supine with face up (figures 1 and 2). In this position, any absolute alcohol escaping into the cerebrospinal fluid around the ganglion rises to its (anatomically inferior but now superior) mandibular branch and so spares corneal sensation in most cases. Furthermore, the supine seems easier than the upright position for patients, many of whom are elderly. After some experience, we devised a method of preliminary placement of the head so that the needle is inserted downward vertically. We simplified and defined more precisely the insertion of the needle and made some new sensory observations after injection. Finally, we produced just enough analgesia to relieve pain and have thus lessened the extent of numbness and the incidence of late distressing paresthesias.

METHOD

Penman[8,9] determined that the needle was to enter the skin at a point selected by preliminary roentgenograms to penetrate the tissues of the cheek and the center of the foramen ovale. Finally the needle was to be advanced in a plane parallel to the anterior surface of the petrous bone 10 to 15 mm. beyond the posterior edge of the foramen ovale, thus lying directly within the posterior root. The position of the needle was determined from roentgenograms made in a special oblique projection and in the submentovertical projection. A trial injection of 0.03 cc. of 2 per cent procaine was followed by a series of injections of 0.05 cc. of absolute alcohol. We have accepted all these aspects of Penman's method.

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Anatomic Considerations

The major neural structure in Meckel's cavity is the *pars triangularis*, that portion of the posterior root which widens and flattens to join the crescent-shaped gasserian ganglion (figures 1 and 3). This so-called triangular part (actually rhomboidal) is about 10 mm. long, 17 mm. wide at its base, and 2 mm. thick. The ganglion is about 4 mm. along the course of the nerve, 18 mm. across, and 3 mm. thick. The intracranial length of the mandibular division measured from the posterior inferior edge of the foramen ovale is 5 or 6 mm.[10] Hence a needle inserted 10 to 15 mm. past the posterior inferior edge of the foramen ovale and directed toward the center of the posterior root (as it crosses the petrous ridge) lies within the "triangular" part of the posterior root.

As one holds a skull with calvarium removed, it is possible to see the petrous ridge when one sights through the region of the cheek and the foramen ovale. That portion of the ridge crossed by the posterior trigeminal root (pars compacta) is usually a clearly defined groove, *incisura nervi trigemini*,[11] the lateral margin of which is more prominent than the medial. The line through the center of the foramen ovale and through a point 2 mm. superior to the middle of the *incisura nervi trigemini* (figures 1, 4, and 5) is the proposed course of the needle. The head is so placed that a needle inserted vertically downward will follow this course. Preliminary radiographs determine this optimum head position and the entry point of the needle.

Preliminary Radiographs

On the x-ray table the patient lies supine on a mattress, beyond which his head can be extended. Two lines are marked on the skin with gentian violet: 1) the orbitomeatal baseline (from the external canthus to the external auditory meatus) on the temple of the involved side, and 2) the midsagittal line of the forehead and nose (figure 2). At the level of the corner of the mouth, midway between the coronoid process of the mandible and the lateral aspect of the maxillary sinus, a violet mark is made on the skin of the affected cheek to indicate the *approximate entry point* of the needle. The grid, modified from that suggested by Penman,[9] consisting of wires 1 cm. apart, making a square, 2 cm. on each side and sandwiched between two pieces of clear film, is now placed on the cheek with its center on the approximate entry point and held by transparent adherent tape.

We follow Penman's suggestion[8] and refer to the angle between the orbitomeatal line and the vertical as the *elevation angle* and that between the midsagittal line and the vertical as the *bearing angle*. These angles are measured with the aid of "angligners," viewed simultaneously by the radiologist and his assistant from the head and side of the table (figure 2). Three preliminary radiographs (anteroposterior oblique views) are now made, each with the central ray directed vertically downward, with the head extended and rotated away from the affected side in the following three positions with the elevation angle and bearing angle, respectively: 65 degrees, 15 degrees; 65 degrees, 20 degrees; 70 degrees, 15 degrees. These radiographs are developed rapidly and the wet films studied while the patient's head is supported comfortably by a pillow. The optimum position of the head is that in which a point 2 mm. above the midpoint of the *incisura nervi trigemini*, corresponding to the center of pars compacta, appears superimposed on the midpoint of the foramen ovale, corresponding to the center of mandibular division. In the average skull, this occurs (figures 1, 2, 4) at an elevation angle of 65 degrees and a bearing angle of 15 degrees. In about half of the cases one of the first three films shows this ideal relationship. If not, additional films are made, with slight adjustments of the head as indicated by comparative study of the first three films. Further radiologic details are presented elsewhere.[12]

When the optimum head position is obtained (figure 4), the *final entry point* is determined from that portion of the grid which superimposes the center of the foramen ovale. The *final entry point* is marked on the skin with a sharp graphite pencil.

Needle Insertion

The skin at the final entry point is sterilized and 2 per cent procaine hydrochloride is injected intradermally. The pillow is removed and, with the aid of angligners, the head is replaced in the optimum position. A 21-gauge 10 cm. long spinal needle (containing its stilet)

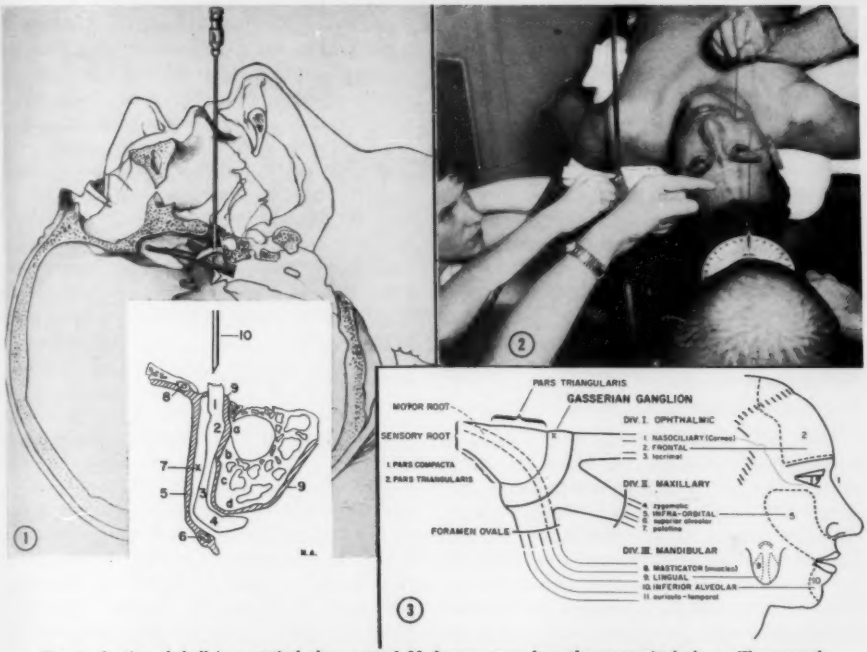

FIG. 1. Section of skull in a vertical plane rotated 20 degrees away from the parasagittal plane. The correctly placed needle lies in this plane. The dotted portion of the needle lies within neural tissue. The gasserian structures have been left intact. With the head in this position, the ophthalmic fibers lie at the lowermost level of Meckel's cavity. *Inset*: Enlargement of petrous portion with the section passing through the gasserian structures. I. Bony markings on anterior surface of petrous pyramid: *a*, bony hiatus (the letter "a" lies in the carotid canal); *b*, impression of gasserian ganglion; *c*, impression of triangular plexus; *d*, groove for posterior root. II. Soft tissues: *1*, mandibular division; *2*, gasserian ganglion; *3*, triangular part of posterior root; *4*, compact part of posterior root; *5*, dural roof of Meckel's cave; *6*, superior petrosal sinus; *7*, cerebrospinal fluid in Meckel's cave lying anterosuperior to gasserian ganglion and triangular part of posterior root; *8*, an intradural vein; *9*, dura on floor of Meckel's cave, adherent to ganglion and extending over base of skull; *10*, needle approaching foramen ovale. In these drawings the bevel of the needle is caudal; for insertion it is preferable for the bevel to be cranial.

FIG. 2. Needle insertion. Radiologist and his assistant are directing alignment of needle.

FIG. 3. Diagram of gasserian ganglion. The branches of the divisions are indicated as they lie in the foramina of the skull. The singly innervated portions of the face are shown on the right. Areas 2, 5, and 10 often do not extend to the median plane.

FIG. 4. Preliminary radiograph (anteroposterior oblique view) with skull in optimal position for injection of right side. The center of the grid is superimposed over the center of the foramen ovale. The notch of the petrous ridge for the posterior root (incisura nervi trigemini) appears just within the lower border of the foramen ovale.

FIG. 5. Radiograph, anteroposterior oblique view. Needle is in the correct position.

FIG. 6. Radiograph, submentovertical view. Needle is in the correct position with tip 15 mm. beyond posterior wall of foramen ovale. Notice diminished density of terminal 10 mm. of needle due to withdrawal of stilet.

is placed in a vertical position with its point down, touching the skin at the final entry point. As it is advanced through the skin and tissues of the cheek, its direction is controlled by vertical angligners (figure 2). As the needle enters the foramen ovale, the patient experiences brief sharp pain in the mandibular division, and the physician feels the resistance and then sudden yielding of the neural tissue at the foramen. The needle is inserted approximately 10 mm. beyond this point of resistance. The stilet is withdrawn to see whether blood or cerebrospinal fluid escapes; these possibilities are considered later.

Radiographic Verification of Location of Needle

If no fluid is obtained, the stilet is replaced and two films are made. The first is taken with the face rotated 5 degrees toward the unaffected side from the position for the anteroposterior oblique view. This *needle anteroposterior oblique view* (figure 5) shows the hub on the film just medial to the needle tip. The second film is the submentovertical view. When made with the stilet withdrawn 1 cm. and held there by the stop suggested by Penman,[9] it permits an accurate measurement of intracranial penetration (figure 6). When the needle passes through the middle of the foramen ovale in the needle anteroposterior oblique view (figure 5) and extends 10 to 15 mm. beyond the posterior wall of the foramen ovale in the submentovertical view (figure 6), it is usually within the posterior root.

Needle Adjustment and Test Injection

If the needle is aligned correctly, its depth can be measured and corrected after pressing a small transparent ruler against the skin alongside the needle and parallel to it. After the needle has been correctly related to the skull, one determines its relationship to the neural tissue by injecting a test dose of 0.03 cc. of 2 per cent procaine (allowing an additional 0.06 cc. for the lumen of the needle). The stilet is always replaced promptly in the needle[9] to prevent blood clotting in the needle's tip. Both touch and pain sensation are tested and recorded. From these data and from the films we try to determine the exact site of the needle tip in relation to the posterior root (figure 3). One must allow for individual variations in the dimensions of the ganglion. Furthermore, procaine diffuses more readily than alcohol within neural tissue. If no numbness results from the procaine injection, the needle is misplaced and requires correction.

If the needle fails to enter the foramen, it will strike the bony undersurface of the floor of the middle cranial fossa at a depth of about 5 cm. from the skin. In such a case, there has been a technical error (usually the patient's head or skin has moved). The needle is withdrawn almost to the skin and reinserted properly.

Blood Emerging from Needle

If blood emerges after removal of the stilet, the needle is slowly withdrawn until blood no longer appears. The needle is cleared with sterile saline solution, the stilet re-inserted, and the depth of the needle checked radiographically (submentovertical view with 1 cm. stop). In our early experience rapidly dripping blood once came from striking the middle meningeal artery at the foramen spinosum. Blood emerging under low pressure probably came from the venous plexus surrounding Meckel's cavity on a few occasions. In some cases it may be possible anatomically to strike the internal carotid artery within the petrous bone.*

Doubly Innervated Areas

Zander[15] showed that many areas of the face and tongue may be doubly innervated. Some examples of double innervation are: 1) somewhat beyond the midline, the tongue or lips may be served by the contralateral nerve as well as the ipsilateral; 2) the lateral area of the cheek may be served not only by the auriculotemporal but also the cervical nerves; 3) the lower lid may be served by branches of both the first and second divisions of the trigeminal nerve. Therefore, these doubly innervated areas may retain sensation after a single portion of the trigeminal root has been adequately denervated for relief of tic douloureux. The singly innervated regions of skin and tongue that can be most usefully tested after gasserian intervention are shown in figure 3.

*Zander, P.: Arch. klin. Chir. 178:242, 1933.

Alcohol Injection

If appropriate (second and/or third division) anesthesia is obtained with procaine, the patient's neck is straightened so that the face is uppermost and the ophthalmic fibers lie in the lowermost portion of Meckel's cavity (figure 1). We place only 0.11 cc. of alcohol in the 1 cc. tuberculin syringe to avoid any risk of excessive movement of the plunger. Harris[7] and Penman[9] use a threaded stem and guard for the plungers of their syringes. A single injection of 0.05 cc. of absolute alcohol is made (always allowing an additional 0.06 cc. for the internal volume of the needle) and the time is recorded. This injection is either painless or causes a brief, mild burning sensation associated with transient flushing of the face. If numbness is obtained (which will take place in four minutes, if at all) we note the quantitative touch and pain sensory responses in the branches indicated in figure 3. As the "shock effect" of the alcohol wears off (usually within 10 minutes), additional injections of alcohol are made as necessary in order to prevent precipitation of tic by pressure on the trigger area, but never more than 0.05 cc. at a time and always with an interval of at least four minutes between injections. The time of each injection and resulting sensory defects are recorded before each additional injection is made. If a disproportionate numbness of the first division occurs, the needle is withdrawn somewhat, the numbness is allowed to wear off, and even smaller quantities of alcohol (0.04 or 0.03 cc.) are injected. We accept Härtel's[6] recommendation of a maximum injection of 0.3 cc. of absolute alcohol; that is, for our purposes, a total of six injections, each 0.05 cc. When sufficient sensory loss lasts 35 to 40 minutes, the needle is withdrawn and the patient is permitted to sit up and go home. If there is corneal anesthesia, the patient is warned against rubbing the eye. He reports for reexamination in a few days and subsequently as indicated.

The fibers of pars triangularis are so disposed (figure 3) that in some of our most recent cases we have succeeded in producing more limited areas of numbness by more accurate placement of the needle. For example, at three progressively deeper positions of the tip of the needle, namely at approximately 10 mm., 12 mm., and 14 mm., minimal alcohol injections have succeeded at times in producing numbness respectively in the third division alone, both second and third divisions, or second division primarily. In the latest 15 cases the numbness of alcohol injections (each 0.05 cc.) required has been respectively: 4, 4, 3, 4, 6, 1, 2, 1, 1, 6, 1, 1, 3, 3, 3. Therefore, in five of our last ten patients a single injection of 0.05 cc. of alcohol sufficed for persistent numbness in the trigger area and relief of pain.

With progressive experience, the duration of the procedure, which formerly was two hours, is now about 55 minutes after the preliminary radiographs have been made.

Cerebrospinal Fluid Escaping from Needle

If cerebrospinal fluid escapes, as it does in about one-fourth of the cases, the triangular part of the posterior root is probably a loose bundle of nerve fibers lying freely within the fluid of Meckel's cavity.* In such a case, one withdraws the needle very slowly until fluid no longer drips from the needle, the tip of which now lies directly in the ganglion itself. Then one rotates the face about 30 degrees toward the unaffected side and, without preliminary procaine, injects 0.05 cc. absolute alcohol. If an adequate area of numbness is produced, but does not last, one repeats this injection as necessary. If an insufficient area of numbness is produced, one may increase the amount of alcohol injected at one time to 0.10, 0.15 or even, rarely, 0.20 cc., always proceeding slowly, checking sensation carefully before deciding to make another injection.

RESULTS

From October 1954 through September 1957 we have used this office procedure for 45 successive patients with tic douloureux (classical trigeminal neuralgia). This series includes all patients seen by us during this period in whom we made the diagnosis and who were willing to undergo any active intervention (injection or operation). Seven of the patients had had previous surgical rhizotomy for this condition. One had had no relief and six obtained temporary relief with recurrence of pain. In all 45 cases numbness was pro-

*Ferner, H.: Die Trigeminuszisterne und ihre praktische Bedeutung für die Alkaholinjektion in das Gassersche Ganglion. Nervenarzt 20:26, 1949.

duced and pain completely relieved, at least temporarily. Usually the patient was amazed by the prompt and complete relief and could hardly believe the routine demonstration that pressure on the former trigger area was now painless. It was not uncommon after injection for the patient to experience a sticking or prickling sensation, which formerly had signaled tic pain. The signal often continued for several days, but usually no pain resulted; rarely very mild tic continued for a few days.

However, in nine of the 45 patients (cases 2, 7, 8, 11, 12, 13, 20, 38, and 40) insufficient alcohol was injected in the correct portion of the posterior root and pain recurred. In eight of these cases another injection was made, six of them within three months. In the other three cases pain recurred after 27, ten, and 11 months, respectively. A recent review of the films in the first seven of these nine cases showed that the needle's position was not correct in four cases, according to our present, more exact standards. In six of these nine patients another gasserian injection was made, in a seventh (case 8 of the series) an infra-orbital injection, and in the eighth, both. The ninth patient is not yet ready to accept another injection. Case 8 underwent surgical rhizotomy after returning to his home in a distant city; none of the other patients in the series has required surgical intervention.

Case 40 had very severe and frequent pain, as well as two unusual features: 1) Overlap of touch sensation (but not pin scratch) from the opposite side to include both upper and lower lips and the skin below the lower lip as far as the angle of the mouth. This was confirmed by numbness being produced only by additional superficial injection of procaine in the median plane. 2) An unexplained delay of a few days in relief of his tic pain which finally departed abruptly and completely. It is doubtful that the second injection was necessary.

There was no serious complication in any case. It was common for a mild headache (responding to aspirin) to be present for a few hours and later painless labial herpes. About half our patients have experienced paresthesias thus far, but only three complained of it bitterly. All of them had been informed that numbness and paresthesia would result. In seven patients (16 per cent) apparently total permanent loss of corneal sensation was produced, but in no case has it led to keratitis nor has tarsorrhaphy been necessary. In one patient (case 17) there was impairment of accommodation and enlargement of the pupil for two days. In another patient (case 13) there was abducens palsy for a few minutes. In a single patient (case 16) there were nystagmus and seventh nerve paralysis for a few minutes. In two patients a hematoma 3 cm. in diameter developed in the cheek, presumably from striking a branch of the internal maxillary artery; however, neither hematoma increased further in size and each intracranial injection proceeded without further ill effect.

DISCUSSION

Penman prefers to produce *complete* loss of touch and pain sensation in the trigger area(s). His patients are hospitalized for three days and are injected while sitting. In 1950 he reported[4] a 97 per cent purely symptomatic success rate in his first 100 radiologically aided injections. The crude relapse rate of tic in the first three years was 6 per cent. Unfortunately corneal anesthesia resulted in 82 of his cases and 15 developed keratitis requiring tarsorrhaphy. In Penman's series both persistent post-injection paresthesias and transitory masticator paralysis were common.

Our method is an office procedure. Since tic varies in severity,[16] we have preferred to relieve it at the expense of the *least* sensory loss which will prevent pain. As our method is less formidable, it offers greater flexibility in meeting the individual needs of each patient. In view of the differences in technic and goal, our results are now restated for comparison with Penman's.[4] Both studies were made at the end of three years of radiologically aided injections for tic douloureux. In our first 45 injections there was a 100 per cent purely symptomatic initial success rate. Twenty-two patients have been followed (usually by telephone or letter) over one year; of these, 11 were followed over two years. The crude relapse rate of tic in the first three years was 20 per cent; however, in eight cases an additional injection again gave relief of pain. The ninth patient is not yet willing to have another injection. Persistent total corneal anes-

thesia occurred in seven cases (16 per cent) but none developed keratitis. About half of our patients complained of post-injection paresthesias, but of these only three (7 per cent) complained with bitterness. All three patients lacked warm human relationships. Two patients had transitory partial masticator paralysis and one (case 40) had complete masticator paralysis. In 13 other cases the masticator muscles were recorded as normal one or two days after injection.

Penman[4] expected that the crude relapse rate in his series after many years would roughly be 10 to 15 per cent. Although our short-term recurrences are becoming less common with improving technic, we expect that our long-term crude relapse rate may continue to be about 20 per cent. As with other methods of attacking the posterior root,[6,17] probably the less anesthesia produced, the greater the risk of recurrence. Nevertheless, as with other methods,[3,7,17] many patients have been permanently relieved of tic without total loss of sensation in the painful area. Certainly for most patients (at least the 80 per cent who will not have recurrence) the savings in care and concern for the eye, paresthesias, temporary masticator paralysis, hospitalization, and (in this country) expenses seem to justify our present method. In the small minority of patients with recurrence, gasserian injection can be repeated promptly and effectively.

Critical comparisons of various radical methods of treating tic douloureux have been published in recent years.[4,5] In discussing electrocoagulation, White and Sweet[5] state (p. 449): "If the proponents of the method perfect it so that they can: 1) consistently destroy the second and third divisions while saving the first and other nearby structures, 2) lower their rate of recurrence, and 3) keep the mortality near zero, many more surgeons will perforce take it up. As far as we know, no one has quite demonstrated this degree of skill. As with alcohol injection, avoidance of denervation of the cornea seems the major unsolved problem." We believe our modification of Penman's method meets these standards and we offer it at this time, at least for those patients with a high surgical risk. Anyone intending to do this delicate and potentially dangerous work should first read the published works of Harris,[2,7,18] Härtel,[6] and Penman.[8,9] Our method requires enough time to proceed deliberately. It also requires complete cooperation from the patient, radiologist, and surgeon.

SUMMARY

A method is described for insertion of a needle into the posterior root of the gasserian ganglion. Preliminary radiographic study determines the entry point of the needle and the exact position of the head required. Then the needle is inserted vertically downward. Further radiographic study indicates the precise relation of the needle to the base of the skull and permits accurate adjustment of its depth. Procaine (2 per cent, 0.03 cc.) is injected to determine the position of the needle within the posterior root (pars triangularis); the needle is further adjusted if necessary. The patient's neck is straightened so that he faces the ceiling squarely. Finally from one to six therapeutic injections of 0.05 cc. of absolute alcohol are made, guided by careful sensory and motor testing. The goal is to prevent further attacks of pain with the least sensory loss. This procedure requires patience, cooperation, and a precise knowledge of anatomy. Over a period of 36 months we have found it safe and effective in relieving tic douloureux in 45 consecutive patients.

We wish to thank Dr. John Penman for much helpful advice in this work. On November 3, 1956 he wrote that he was using nitrous oxide anesthesia for the insertion of the needle and, independently, started to use the supine position of the patient for the injection of alcohol. In March 1958 he wrote that he is performing this work on outpatients. He believes that the most important paper written on the subject of trigeminal injection is Haertel, F.: Die Leitungsanaesthesie und Injectionsbehandlung des Ganglion Gasseri und der Trigeminusstaemme (Arch. klin. Chir. 100:193, 1912). The patients who have been cured of tic douloureux but who complain of dysesthesias are discussed by Dr. Penman in "Pain as an Old Friend" (Lancet 1:633, 1954).

The angligner is a protractor with an extended stylus, manufactured by the General Electric Company.

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■ The duration of infantile paralysis is very variable. It may pass off in a few days, or even a few hours: it is more likely to occupy several weeks or months in this process of improvement. Improvement, to a greater or less degree, is indeed the rule, and not the exception; and it may even be said that the cases which stop far short of recovery are by no means common. Mr. Adams says, "It is generally supposed that, unless recovery takes place within a few months, the paralysis is persistent through life; but I have seen many cases in which improvement has proceeded, to a very useful extent, several years after the seizure;" and to the truth of this remark my own experience bears ample testimony. Indeed, I should say from what I have seen, that if the paralyzed muscles retain their electro-contractility and electro-sensiibility, and so show that they have not passed into that state of fatty degeneration into which they always tend to pass eventually, there appears to be scarcely any limit to the time in which improvement, and even complete recovery, is possible.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Relationship of dystrophia myotonica (myotonic dystrophy) and myotonia congenita (Thomsen's disease)

J. E. Caughey, M.D., F.R.C.P., F.R.A.C.P.

PROBABLY the first account of myotonia was written by Sir Charles Bell,[1] who described it as follows: "The most common instance of this is an impediment in speech, when the consent of muscles is imperfect, but this sometimes extends to all the muscles of the body. I find that some are capable of lifting a heavy weight or of walking 15 or 20 miles and yet they have not the proper command of their limbs. There is an insecurity and want of confidence in the motions of the body, which overtake them on any excitement – a paralysis of the knee which prevents them from putting one leg before the other and which endangers their falling. Thus a gentleman capable of bodily exertion, on going to hand a lady to the dining-room will stagger like a drunken man, and in the streets any sudden noise or occasion for getting quickly out of the way, will cause him to fall down and in this manner a want of confidence produces a nervous excitement which increases the evil. With confidence, the power of volition acts sufficiently. There is neither defect of speech or irresolution in the motion of the limbs when the person is at ease or under a flow of spirits." It seems, too, that Bell[1] was aware of the improvement in myotonia following ingestion of alcohol.

Most authors, however, give credit for the first description of myotonia to Leyden,[2] who described a condition which was soon to be known as Thomsen's disease. Thomsen's[3] account gained general recognition for the symptom of myotonia. Erb's monograph[4] stimulated great interest in myotonia and several papers followed with accounts of myotonia congenita and of some atypical examples in which muscle atrophy was associated with myotonia. Among these latter accounts, Dana[5] deserves mention, but it is probably Déléage[6] to whom is usually given the credit of reporting the first case of dystrophia myotonica.

Since then there has been variance of opinion as to the relationship, if any, of myotonia congenita and dystrophia myotonica. Originally dystrophia myotonica was regarded as a variant of myotonia congenita, and Rossolimo[7] suggested that cases presenting both myotonia and muscle atrophy should be regarded as special variants of Thomsen's disease. In 1909 two important contributions[8,9] appeared. While Batten and Gibb[8] maintained they were distinct disorders, Steinert[9] believed that cases with atrophy originally presented as typical cases of Thomsen's disease.

Maas and Paterson[10] reviewed the literature to date and showed the wide variance of opinion. Thus Adie and Greenfield,[11] Nissen,[12] Nevin,[13] and others regarded the two diseases as quite distinct, whereas Guillain, Bertrand and Rouques,[14] Maas,[15] and others maintained they were a single entity. Maas and Paterson[10] affirmed that myotonia congenita is but a variant of dystrophia myotonica. Adams, Denny-Brown, and Pearson[16] classified myotonia congenita separately as an inherited anomaly of muscular contraction and not a dystrophy. Thomasen[17] questioned Maas and Paterson's[10] interpretation of the literature and stated that they had no cases that could be labeled Thomsen's disease, but only cases of dystrophia myotonica. Thomasen[17] went to some length to prove that the two diseases are not identical.

In the past ten years, we have had the opportunity of studying 40 cases of dystrophia myotonica in the Auckland and Otago provinces[18–25] in New Zealand. No family with myotonia congenita (Thomsen's disease) was

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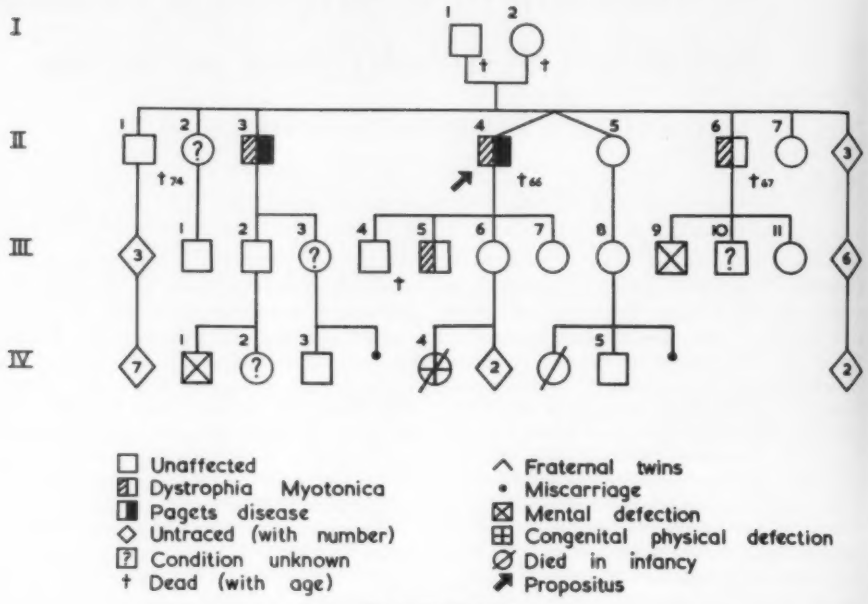

FIG. 1. Family tree.

observed until 1955. This family, which we now report in some detail, we believe is of importance, since older members have undoubted dystrophia myotonica, whereas a member of the second generation presents a picture of myotonia congenita. Thus, the family gives some support to those who contend that so-called myotonia congenita is but a variant of dystrophia myotonica and not a separate disease entity.

CASE REPORTS

Case 1. (II, 4 in figure 1) A 66 year old retired employee of the Dunedin City Council fell in 1951 and fractured his right femur at the site of a lesion of Paget's disease. He was admitted to the hospital and made an uneventful recovery. Three years later he was readmitted and stated that three weeks previously he had developed pains in the spine in the mid-dorsal region which radiated around his abdomen at the level of the umbilicus. These persisted and five days before admission he developed numbness of the toes and weakness of both legs. For three weeks he had had difficulty in urination.

The history revealed that he had started to become bald when 17 or 18 years old, and he stated he had noticed difficulty in relaxing his grasp as long as he could recall. He had noticed his leg muscles were stiff and in cold weather he was inclined to fall. From youth until middle life his limb muscles had been very large, although he realized he was not abnormally strong. He had never complained of weakness apart from the disability occasioned by the "stiff" muscles. There had been no impairment of sex function and his vision had deteriorated very little.

On examination he was a well developed elderly man with frontal baldness. He had bilateral cataracts. The temporalis muscles were wasted. He had mechanical myotonia of the tongue. The anterior cervical muscles were somewhat wasted and neck flexion was weak. The neck extensors were strong. There was hypertrophy of the forearm muscles. There was moderate myotonia of the grip on either side and mechanical myotonia of the thenar and hypothenar muscle groups. The power was average, but less in the arms than would have been expected.

His abdominal muscles were very weak. He was unable to sit up with arms folded across his chest. He had loss of sweating and loss of appreciation of pain, heat, cold, light touch, and vibration up to a level of D_{10} segment. The upper abdominal reflexes were present, the lower were absent.

In the lower extremities the muscles of the calves and thighs were large. There was mechanical myotonia of the calf muscles. All muscle

FIG. 2. *Case 1.* Wasting of temporalis and anterior cervical muscles; frontal baldness.

FIG. 3. *Case 1.* Right sternomastoid muscle showing variation of muscle size, multiplication of nuclei, and increase of fibrous tissue.

groups were weak, especially the gastrocnemic muscles. The deep reflexes in the arms were all present, but in the lower extremities all deep reflexes were increased and the plantar responses were extensor in type.

The prostate gland and testes were normal to palpation.

Laboratory studies. Radiography of the lumbar spine, pelvis, and skull revealed Paget's disease involving most of the vertebrae and the pelvis. The skull showed thickening of the calvarium, Paget's disease of the frontal bones, extensive frontal sinuses, and a normal pituitary fossa. There had been some enlargement and compression of the lumbar and thoracic vertebrae, causing some encroachment upon the neural canal. This was most marked in the upper lumbar region. The left clavicle and both femora had manifest evidence of Paget's disease.

Two days after admission his legs became progressively weaker and the sensory impairment more complete. In view of the clinical and radiologic findings, a diagnosis of spinal compression was made and no myelography was considered necessary. Laminectomy was carried out at the level of T_{8-12}. When the upper two laminae were removed there was a large extradural mass arising from the lamina and enveloping the dura. This was most marked on the left side and the pedicles and bodies were involved. It seemed apparent that there was sarcomatous change at the site of the Paget's lesion.

Following operation the muscle power slowly returned, but he became incontinent of urine and an indwelling catheter became necessary. He continued to make good progress in walking, but two months after the operation he slipped and fell in the hospital and fractured his right femur. Radiography revealed a pathologic fracture at the site of a Paget's lesion. The leg was splinted with traction, but in the course of the next two months his general condition deteriorated and he developed three large soft swellings over the vertex. He deteriorated rapidly and died in April 1955.

Post Mortem. The temporal muscles were wasted. The forearm and calf muscles were very well developed. The skull was thickened, soft, and brittle. Three separate expanding lesions were observed in the vault varying from 4 to 8 cm. in size. Histologic examination revealed in all sections the irregular thick trabeculae of Paget's disease. In the neoplastic areas the marrow spaces were filled with solid sheets of spindle-shaped and round cells characteristic of an osteosarcoma. There was some formation of tumor bone; osteosarcomatous deposits were seen in the dura in relation to the skull lesions.

Muscular system. The sternomastoid muscles showed marked atrophy and the gastrocnemic, quadriceps, and vertebral muscles appeared pale. Histologically the sternomastoid muscles showed severe changes. The fibers varied considerably in size and were separated by broad strands of collagen. Degenerative change was seen in the fiber cytoplasm, with loss of striations, vacuolation, and uneven staining reaction. Islands of adipose tissue were seen in many sections. The gastrocnemic muscles showed marked fibrous replacement in some of the sections. Only a few atrophied fibers remained and these were separated by dense col-

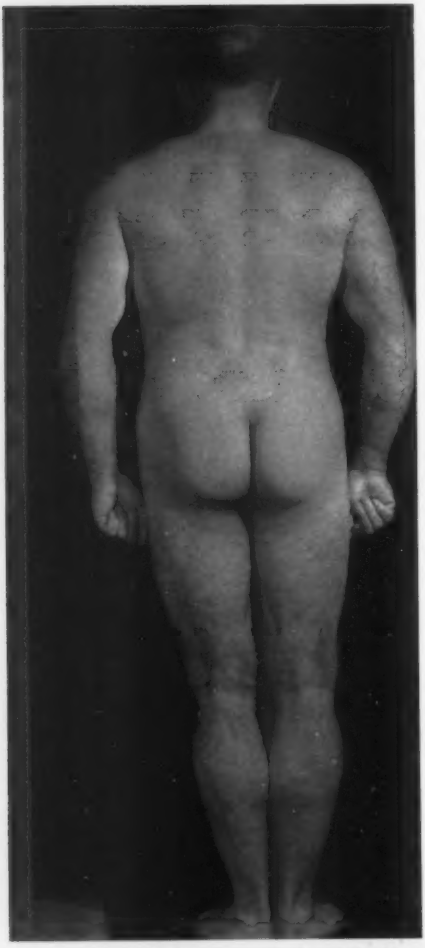

FIG. 4. *Case* 3. Baldness; hypertrophy of shoulder girdle muscles, forearms, and calves.

lagen. The quadriceps muscles showed negligible scarring and there was great variation in the fiber size. The arm flexors showed variation in fiber size, with varying degrees of sarcoplasmic degeneration. A striking feature was the presence of a number of fibers which were represented by a peripheral zone of homogeneous cytoplasm, the center of the fiber being empty.

Skeletal system. The vertebral column was removed, deep frozen, and sectioned sagittally through the spinal canal. The lower thoracic and upper lumbar vertebrae were expanded irregularly and there was infiltration of the vertebral muscles by tumor. The cut surfaces of the vertebrae were pale and mottled and of soft texture. The neoplastic process had invaded and encroached upon the spinal canal, with compression of the cord in the lumbar region. The inner two-thirds of the left clavicle were diffusely expanded, measuring 4 cm. in diameter. The right femur was expanded and the cortex irregularly destroyed with infiltration of the muscles by tumor. There was extensive neoplastic change at the site of a healed fracture near the middle of the shaft.

Histologically in all the bones described the features of Paget's disease could be recognized. Thick irregular bony trabeculae showing the characteristic haphazard mosaic pattern were prominent. The marrow spaces were filled by neoplastic spindle and round cells with occasional tumor giant cells. Tumor bone was also prominent in some of the sections. Similar sarcomatous deposits were seen in the vertebral and thigh muscles.

The testes were of normal size, and histologic sections revealed a diffuse fine scarring, although seminiferous tubules showed only minor atrophy.

Case 2. (II, 3 in figure 1) A 67 year old retired government official was struck by an automobile when alighting from a tramcar and dislocated his right hip in 1951. He was admitted to the Dunedin Hospital where the dislocation was reduced. While in the hospital he complained of pain in the left hip, and radiographs revealed Paget's disease of the left femur with associated osteoarthritis. The lumbar vertebrae and pelvis were also affected with Paget's disease. Radiographs of the skull revealed a normal pituitary fossa and normal pneumatization of the sinuses. However, there was generalized thickening of the calvarium. No definite evidence of Paget's disease was seen in the skull.

When interviewed in 1955 during an investigation of this family, he stated he had noted difficulty in relaxing his grasp as long as he could remember. He noticed some difficulty getting up from a chair because of "stiffness," and when playing bowls he sometimes had difficulty relaxing his grasp of the wood.

On examination he had frontal baldness and marked leukoderma of the face and limbs. There were bilateral lenticular opacities with cuneiform clefts and streaks, and there were also numerous grey punctate opacities throughout the anterior lens cortex and a few in the posterior cortex. No angioid streaks were seen in the retina. There was mechanical myotonia of the tongue and of the small muscles of the hands in the thenar and hypothenar eminences. There was voluntary myotonia on gripping which disappeared after repetitive grasping. The facial muscles were normal. There was weakness of the neck flexors and of the abdominal muscles. He had difficulty sitting up from the lying position. There was little wasting of the forearms. The deep reflexes were all present. There was no obvious gonadal atrophy.

The diagnosis was dystrophia myotonica of a mild degree, with associated Paget's disease of bone.

Case 3. (III, 5 in figure 1) A 35 year old printer was interviewed during the investigation of the family. At the age of nine years he noticed difficulty with "stiff" muscles and once, when starting to run in a race, he fell because of tightening of his leg muscles. He had noticed difficulty relaxing his grasp all his life, but this had caused little inconvenience. He was aware that this myotonia was relieved after taking alcohol. He started to go bald at age 20. As a younger man he did a lot of wrestling. He had always had large muscles, but, although fairly strong, he was aware his strength was not in proportion to the size of his muscles.

On examination he had frontal baldness and was very muscular. The lenses were normal to direct examination. No slit lamp examination was made. There was mechanical myotonia of the tongue and of the thenar and hypothenar eminences. He had well marked myotonia of the grip which passed off after gripping three times. There was some hypertrophy of the masseter muscles but no facial weakness. The neck flexors and extensors were strong. The biceps muscles and the forearm muscles showed marked hypertrophy. The power was moderately good and equal, but not in keeping with the size of the muscles. There was pseudohypertrophy of the thigh and calf muscles and mechanical myotonia of the calf muscles. Power was not commensurate with the muscle size. All deep reflexes were present and equal. The gonads were normal to palpation and radiographs of the skull and pelvis were normal.

DISCUSSION

Case 1 in this family had some muscle wasting, frontal baldness, bilateral lenticular opacities, voluntary and mechanical myotonia, and weakness of the abdominal muscles and of the anterior cervical muscles. The diagnosis was confirmed at post mortem when typical degenerative changes were found in the sternomastoid muscles and in the gastrocnemic muscles. Some muscles showed a degree of pseudohypertrophy. No gonadal atrophy of note was found.

In case 2 frontal baldness, cataracts, and well marked myotonia of the grip and the tongue were apparent, and there was weakness of the abdominal muscles and cervical muscles, but no obvious wasting or gonadal atrophy. The skull showed thickening of the calvarium.

In case 3, a son of case 1, the picture was that of myotonia congenita with widespread muscle hypertrophy and widespread myotonia. There was no wasting or weakness and no gonadal atrophy. He was prematurely bald in the frontal region. There were no lenticular opacities. The skull was normal.

Thus, it could be argued that in this family there are two cases of dystrophia myotonica and one of myotonia congenita occurring coincidently. On the other hand, it would be more reasonable to suggest that we are dealing with different phases of the same disease. Some consideration will be given in turn to the symptoms and signs encountered in dystrophia myotonica and myotonia congenita.

MYOTONIA

The age at which myotonia becomes apparent has been considered significant in differentiating Thomsen's disease and dystrophia myotonica. Thomsen,[3] Nissen,[12] and others have maintained myotonia may be congenital in Thomsen's disease, manifesting itself as difficulties in suckling and as prolonged contraction of the orbicularis oculi muscles when the face is washed in cold water.

The interpretation of these observations must be difficult and somewhat open to question. Thomasen[17] found no myotonia in infants, but stated it may occur in early childhood at three to four years. He reports that one child in a family with dystrophia myotonica had mechanical myotonia at two years and active myotonia at four years.

We have observed active and mechanical myotonia in a boy aged 12 years, the son of a woman with dystrophia myotonica. The boy had dystrophia myotonica with congenital physical and mental defects.

In the family reported above, case 3 stated he first became aware of active myotonia at the age of nine years when starting in a flat race. In wasting muscles, myotonia becomes less and less apparent until it disappears. In Thomsen's disease myotonia varies from case to case; while it may be localized to the legs or grip, on occasion it may be spread widely to affect all skeletal muscles. It is reported it may affect facial and ocular muscles, which becomes apparent on firm closure of the eyes. We have not observed this, but we have observed it in the respiratory muscles on deep inspiration in one patient with myotonia congenita. The most common site of active myotonia in Thomsen's disease is in the grip, and

mechanical myotonia is most commonly seen in the thenar muscles and in the tongue. Active myotonia is commonly present in the thighs and legs, which accounts for many unexpected falls.

Myotonia in dystrophia myotonica is usually reported to be less widespread, affecting the grip only. We believe this may be due to the degree of wasting which is usually present. In our experience, evidence of active myotonia in the legs causing falls is a very common feature of dystrophia myotonica; in time, such patients are usually confined to their homes for fear of falls, and in the quieter atmosphere of the home the falls occur but rarely. We have observed widespread mechanical myotonia in the tongue, hands, arms, glutei, thighs, legs, and feet muscles.

The phenomena of so-called paramyotonia, which is the aggravation of myotonia by cold, has often been observed in dystrophia myotonica, and it was apparent in case 3 with myotonia congenita. Our experience in this regard coincides with most observers, and we do not believe there is justification for the separation, as suggested by Eulenburg,[26] of paramyotonia as a separate entity.

In our experience then, we do not believe the two diseases can be differentiated by the extent and location of the myotonia, although in general it seems that myotonia is usually more widespread in Thomsen's disease, but this may be due to relatively little muscle wasting.

PSEUDOHYPERTROPHY

This is almost invariably a feature of myotonia congenita, but it is well recognized as occurring in dystrophia myotonica in localized muscle groups. Out of 40 well documented cases of dystrophia myotonica, we have observed it four times. In case 1, who had always had big muscles, there was a suggestion of hypertrophy of forearm muscles at age 66. In case 3, however, the hypertrophy or pseudohypertrophy was widespread, affecting muscles of mastication, shoulder girdles, upper arms, forearms, hands, glutei, thighs, and legs. Hence, in myotonia congenita pseudohypertrophy is usually widespread, whereas in dystrophia myotonica it occurs infrequently and then in isolated muscle groups only.

MUSCLE ATROPHY AND WEAKNESS

These are characteristically seen in dystrophia myotonica and, in our experience, especially involve facial muscles, anterior cervical muscles, trunk flexors, forearms, and quadriceps and dorsiflexors of the feet. In case 1 there was some wasting in the face and neck and objective weakness; on testing, there was weakness of the anterior cervical muscles and trunk flexors, and histologic section confirmed the atrophic lesion. In case 1 there was pseudohypertrophy of muscle over many years, but in later life, muscle wasting developed and it seemed a transition had occurred from so-called myotonia congenita to dystrophia myotonica.

CATARACT

Cataract is perhaps the most characteristic general dystrophic feature in dystrophia myotonica. In Thomsen's disease, on the other hand, cataract is not reported as a feature. Maas and Paterson[10] stated that slit lamp examination was unknown when Thomsen[3] reported his cases. Thomasen[17] reported on slit lamp examinations in eight of his patients with myotonia congenita, four of these, aged 34, 27, 19, and 39 years, had lenticular opacities which were small and not characteristic. Three of these were in members of the family studied by Thomsen.

In two of our cases, slit lamp examination revealed lenticular opacities. We have seen one other man aged 52 years with myotonia congenita, in whom slit lamp examination revealed a few white scintillating opacities just deep to the zone of disjunction.

We have not observed other dystrophic phenomena, apart from the thickened calvarium in case 2. The recently described radiologic changes in the skull in dystrophia myotonica[18,19,24] suggest an interesting study of all available patients with myotonia congenita which may establish a further link between these two disorders.

COURSE

Maas and Paterson[10] maintained that there are a limited number of cases of myotonia congenita which, on reexamination after an interval of some years, have shown definite signs of dystrophia myotonica. Our two patients

reported above appear to illustrate this same feature.

All observers agree that muscular dystrophies are a group of heredofamilial disorders. A number of different forms have been recognized, owing to variations in the distribution of the muscles affected. In addition to muscle dystrophy, there is associated a contractile disorder of muscle in the form of myotonia in some cases, and in others, a series of dystrophic features such as cataract, gonadal atrophy, skull changes, and congenital defects. Affected muscles may show atrophy, true hypertrophy, or pseudohypertrophy in the different forms of the disease, even in the same patient.

The mode of inheritance is not clear. In some, it is sex-linked, as in pseudohypertrophic muscular dystrophy, and in some, it is clearly dominant. In others, more complicated modes of inheritance have been evoked to account for the findings in certain families.

Given forms of dystrophy usually breed true, but intermediate forms occur and most families with dystrophy have combinations of signs and symptoms peculiar to themselves. This generalization can be applied to the myotonic dystrophies, myotonia congenita and dystrophia myotonica. There are various combinations of myotonia, atrophy, hypertrophy or pseudohypertrophy of muscles, gonadal atrophy, and skull changes. Some families with dystrophia myotonica, in our experience, may be free of cataract, and some have a high incidence of cataract. The same can be said of the bony changes in the skull. In Thomsen's family[3] which has been so fully studied, the clinical picture was dominated by the myotonia and hypertrophy or pseudohypertrophy. There were no gonadal changes and thus there was nothing in this family to bring about progressive deterioration, hence the family goes on.

In our family reported above, we appear to have an intermediate form, presenting some features peculiar to the two recognized forms of myotonic dystrophy. It might be argued that this family gives support to the suggestion that myotonia congenita is an early stage of dystrophia myotonica. On the other hand, it can be regarded as an intermediate form which forms a link between the two recognized forms of myotonic dystrophy. This variation in form is likely to be determined genetically. This view seems to be the most reasonable way to account for the unexplained features of these myotonic dystrophies.

SUMMARY

There is wide variance of opinion concerning the relationship, if any, of dystrophia myotonica and myotonia congenita.

An account is given of a family in which two older members had dystrophia myotonica, and a member of the second generation presented with a picture of myotonia congenita.

Various symptoms and signs common to the two disorders are discussed.

The family reported appears to be an intermediate form between the two recognized forms of myotonic dystrophy. This variation in form is likely to be determined genetically and is peculiar to this particular family. Such families might well explain the divergence of opinion as to the relationship between the two disorders.

The author wishes to thank Dr. A. Veale for help in the genetic aspects of this paper and Dr. B. Heslop for the pathologic sections. Also he is indebted to the photographic department of the Otago Medical School for the photographs and to Miss J. Smith for secretarial assistance.

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■ In epilepsy, all of the muscles may be violently and involuntarily thrown into the various actions of which they are capable in a state of health, and when subject to the will. Those of the breast and abdomen are sometimes most powerfully affected with spasm, so that, emprosthotonos, or opisthotonos, or the general rigidity of tetanos, supervene. Boerhaave remarks, that there is no gesture, distortion, or posture, which epilepsy has not sometimes represented. It imitates all kinds of motion; running, walking, whirling round, falling prostrate, &c.—What Sydenham has said of hysteria, respecting the difficulty of describing all the symptoms which occur in its different forms, may be truly said of epilepsy.

In the paroxysm, the symptoms above mentioned, sometimes sooner, sometimes later, gradually give way. The convulsions become less violent, the breathing more free, the pulse more full, slow, and regular, the countenance more composed, and the patient falls into a state of somnolency or profound sleep, on awakening from which, he by degrees returns to his usual state, nothing more than languor or lassitude remaining.

John Cooke in *A Treatise on Nervous Diseases,* published in 1824.

Localization within the amygdaloid complex of anesthetized animals

Charles D. Wood, Ph.D., Byron Schottelius, Ph.D.,
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A NUMBER of physiologic functions have been reported to be influenced by the amygdaloid complex.[1,2] Histologic studies demonstrate that this nuclear complex is composed of at least seven distinct nuclei.[3] From a developmental standpoint, these nuclei can be separated into two groups, the corticomedial division and the basolateral division.[4] These nuclei are also known to vary in their relative development with animals higher in the phylogenetic scale. These facts suggest the possibility that the component nuclei may be functional entities. Kaada[5] and Koikegami[6] have presented some evidence of functional localization within the complex, but otherwise there has been little experimental evidence to indicate such localization.

If localization of function to the component amygdaloid structures is to be demonstrated, precautions against spread of stimulation currents to adjacent structures are necessary. In this study measures were taken to minimize this factor.

METHODS

In this study 50 male Sprague-Dawley rats of 200 gm. average body weight were used. A deep level of ether anesthesia was maintained throughout the procedures. The scalp was opened in the midline, burr holes were produced in the appropriate areas of the skull, and the dura was reflected from the operative site. The animals were placed in the Kreig-Johnson stereotaxic apparatus. A stainless steel monopolar electrode insulated except at the tip with Tygon paint was then positioned in the desired area. The indifferent electrode was clipped to a foot. Respiratory responses were recorded with a pneumograph and smoked drum. Blood pressure alterations were recorded by means of the Friedman-Freed tail cuff and microphone arrangement.[7]

A total of 25 cats and eight monkeys were also used in this research. A deep level of anesthesia was established with sodium pentobarbital at least two hours prior to surgery and maintained throughout the procedures. The animals were prepared in the same manner as described above. A Lab-Tronics stereotaxic apparatus was used to position bipolar or coaxial electrodes. Blood pressure alterations in the cat experiments were recorded from a cannulated femoral artery.

A Grass S-4 stimulator was used in all experiments. Stimulation parameters of 2.5 milliseconds duration and 60 cycles per second were maintained in all procedures. The amplitude of the stimulation was slowly increased in successive stimulations until the threshold of the response being investigated was reached for each area.

RESULTS

Pupillary dilatation. In cats and monkeys bilateral pupillary dilatation was more pronounced and could be obtained at the lowest threshold (1 to 2 volts) in the central portion of the medial nucleus. With higher stimulation intensities this response was readily obtained from all parts of the complex.

Eye movements. Bilateral rolling or turning of the eyes inward, as if to become fixed on a point directly forward, was observed when the amygdaloid area was stimulated. This response was obtained at lowest stimulation intensity (2 volts) in the region of the medial nucleus in the cat and monkey.

Nictating membrane. The nictating membrane was extended over the pupil bilaterally

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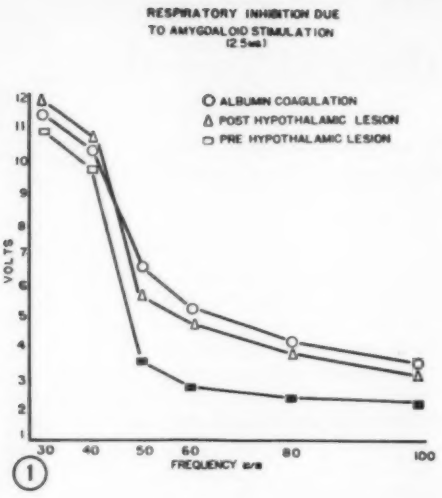


FIG. 1. Respiratory inhibition in the rat produced by stimulation of the medial amygdaloid area. Rectangles represent stimulation parameters required prior to hypothalamic lesions to produce complete cessation of respiration for at least 10 seconds. Triangles represent parameters required for similar inhibition subsequent to lesions placed in the region of the ventromedial hypothalamic nucleus. Circles represent threshold for coagulation of egg albumin for these same stimulation parameters. Solid symbols indicate statistically significant differences ($P = .05$) between coagulation threshold and parameters required to inhibit respiration. Pulse duration was maintained at 2.5 milliseconds in all procedures.

with stimulation amplitude of 2 to 3 volts. This response was difficult to localize, but it appeared to be most prominent in the corticomedial division.

Respiratory inhibition. Stimulation of the medial nucleus of the rat with an intensity of 3 volts produced inhibition of the inspiratory phase of respiration. If this stimulation continued unchanged, escape from inhibition was observed after a period of approximately 10 seconds and normal rhythm and amplitude were reestablished. No alteration was seen when the stimulation was then terminated. A stimulation amplitude of 5 volts in the lateral nucleus gave a less pronounced inhibition.

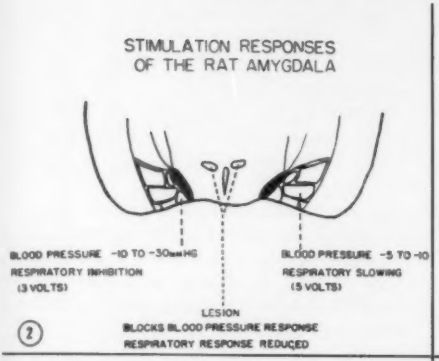
In the cat and monkey the lowest threshold for this response was observed to be in the cortical nucleus. Lesions placed in the region of the ventromedial nucleus of the hypothalamus raised the threshold for this response but did not eliminate it.

Blood pressure responses. With deep anesthesia a fall in blood pressure was consistently produced by stimulation of the amygdaloid complex. In conscious or lightly anesthetized animals this response was quite variable. Stimulation of the corticomedial division in the rat with an intensity of 3 volts elicited a fall in blood pressure averaging 20 to 30 mm. Hg. Intensities of 5 volts in the basolateral division produced a fall in blood pressure which averaged only 10 mm. Hg. Bilateral lesions placed in the region of the ventromedial nucleus of the hypothalamus abolished these responses.

Movements of the face and jaw. Lowest thresholds for movements of the face and jaw were found in the basolateral division. The ventral portion of the lateral nucleus appeared to be the area with the lowest threshold (3 volts) for jaw closure. An area was found in the basal medial nucleus of the cat which, on stimulation (3 volts), gave an initial response of sustained jaw opening; as the intensity of stimulation was increased (4 volts), the response changed to one of sustained jaw closure. Movements of the lips and face appeared to be most prominently represented in an area just dorsal to the areas for jaw movement and required intensities of 3.5 to 4.5 volts.

DISCUSSION

In the cat the amygdaloid complex is a very compact area, with maximum dimensions of less than 1 cm. Stimulation with high intensities might be expected to activate all parts of this area. This is supported by the fact that responses elicited from this area can be produced from all parts of the complex and from the adjacent temporal lobe areas if the inten-



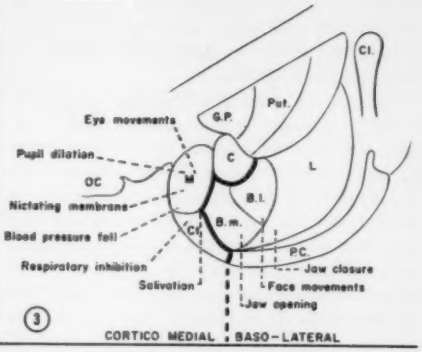


FIG. 2. Cross section through the amygdaloid areas of the rat brain, illustrating stimulation points in the medial and lateral amygdala, as well as lesion areas in the hypothalamus.

FIG. 3. Cross section through the amygdaloid complex of the cat, showing areas of lowest threshold for various responses.

FIG. 4. A schematic representation of the amygdaloid complex of the monkey, showing the areas of lowest threshold for responses obtained by electrical stimulation. Each structure shown is intended to indicate the area of lowest threshold for the responses associated with that structure and not a point to point relationship. (Compare with the figure 3). Relative size of each structure indicates the relative prominence of these responses.

sity of stimulation is high enough.[8] In the present study a deep level of anesthesia was maintained for two or more hours before the stimulation procedures. By this method it was hoped that the adjacent areas would be maximally depressed and, therefore, less susceptible to spread of stimulation currents.[9] To further guard against current spread, minimal intensities of stimulation were used. This allowed the lowest threshold for each response to be determined for each area.

The basolateral division of the complex appears to mediate the movements of the face and jaw. An area in the basal medial nucleus had the lowest threshold for the response of jaw opening, while the lowest threshold for jaw closure was found in the lateral nucleus. These findings indicate that there may be separate centers for these movements which would necessarily act together in such coordinated functions as chewing. Facial movements also appeared to be localized to the basolateral division. It is interesting to consider the possibility that this latter finding may be related to the fact that this portion of the amygdaloid complex reaches its greatest relative development in the animals highest in the phylogenetic scale and that these animals possess the most expressive faces in emotional reactions.

The corticomedial division gave stimulation responses which were related to the autonomic system. The blood pressure, respiratory, and eye responses elicited from this area indicate that it may be concerned with coordination of the autonomic system with the somatic and emotional responses produced by stimulation of amygdaloid areas.

Bilateral lesions of the ventromedial nucleus of the hypothalamus abolished the blood pressure responses and raised the threshold for respiratory inhibition. Therefore, the impulses influencing these functions would appear to be mediated through or pass in the region of this hypothalamic structure.

No localization of the divisions of the auto-

nomic system within the corticomedial area was possible, since both sympathetic and parasympathetic responses were obtained from the same stimulation sites.

The responses elicited from the amygdaloid complex appeared to be related to this area and not due to spread to adjacent areas. In addition to the precautions already mentioned, the middle cranial fossa was dried with suction and the temporal lobe was retracted from contact with the dura before stimulation in a series of animals. Responses were the same under these conditions as before. The location of areas of lowest threshold for somatic movements in the ventral portion of the complex would argue against spread of current to the internal capsule. Lowest threshold for the eye responses was in the central portion of the medial nucleus rather than adjacent to the optic tract. The possibility that optic fibers related to Meyers loop pass through this area and may be responsible for these reactions, however, has not been eliminated.

The results of this investigation indicate that some localization of function to the component areas of the amygdaloid complex is possible. These responses do not appear to be due to spread of stimulation current to adjacent structures.

CONCLUSIONS

1. The corticomedial division of the amygdaloid complex appears to be the area concerned with regulation of autonomic responses from this region.

2. The blood pressure responses from the amygdaloid area appear to be mediated through the region of the ventromedial nucleus of the hypothalamus. Respiratory responses from the amygdaloid complex also appear to be associated with this structure.

3. The basolateral division appears to be concerned with the somatic responses reported from this area, especially with movements of the face and jaw. Sustained jaw opening was obtained at lowest threshold from the basal medial nucleus, and the lowest threshold for jaw closure was found to be in the lateral nucleus.

4. The reactions elicited by stimulation of the amygdaloid complex appear to be a function of this area and not due to spread of stimulation current to adjacent structures.

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Vertebral deformities and other anomalies in Charcot-Marie-Tooth disease

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CHARCOT-MARIE[1] AND TOOTH[2] in 1886 described independently the disease entity characterized by the onset in childhood of atrophy of the muscles of the distal portion of the extremities, with an associated mild sensory deficit and a strong familial background. Since then many case histories with genealogies have been recorded, and it is now well known that there are deformities of the hands and feet, that the disease has no effect on life expectancy, and that the genetic pattern is usually dominant, though it may be recessive or sex-linked. While vertebral deformities, particularly kyphoscoliosis, have been a frequent finding in other hereditary diseases, Charcot-Marie-Tooth disease has been virtually free of these and other anomalies, despite the strong genetic factor in the etiology.

This paper concerns a group of nine siblings, among whom there were three cases of Charcot-Marie-Tooth disease with severe kyphoscoliosis, one case of congenital heart disease with imperforate anus, and one still-birth with a lumbosacral spina bifida in five different siblings, parents of whom were first cousins but unaffected themselves. The family is part of a genealogy traced back for six generations in which there was a mixed genetic pattern, predominately dominant, plus consanguinity and additional genetic influences associated with other abnormalities. In presenting this family a genetic factor in the etiology of vertebral deformities evolves.

MATERIAL

All of these people were or are from an extremely isolated and inaccessible mountainous community in northern New York state. All members are descended from two sisters who married two of the earliest settlers who came there shortly after the Revolutionary War. The information was obtained from multiple interviews and examinations of the immediate family, unaffected members of the pedigree, remotely related elders, unrelated community elders, birth and death certificates, the town historian, and the New York State Genealogical and Historical Library. All information herein was checked and cross-checked on several occasions. Any contradictory or doubtful information was not included in this study. However, due to absent and destroyed records, failing memories, and considerable resistance among members of the family to uncovering a hereditary disease, a complete pedigree was not obtained.

All members of this pedigree, including those affected with Charcot-Marie-Tooth disease and excluding the present generation, have lived to the age of 55 and the great majority to 65 or more. As far as it is known from existing family history and state death certificates, this disease has not been a contributing factor in any death.

Case 1 provoked this investigation because of the associated defects of marked kyphoscoliosis, epilepsy, mental and personality deficits, plus a firm denial of family history. It is of interest that, even after the genetic influence was demonstrated, most of the members of this family insisted that the defects were due to other causes such as falls, "chronic polio," being "marked" during pregnancy, and the like. Additional findings in all siblings of this group included marked ectomorphism, a mild right lower facial paresis, and impairment of convergence. An uninvolved sibling (V, I) had

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seizures, hypoplasia of the right upper body, and a diffusely abnormal electroencephalogram.

The mother, aged 53, a mesomorph body type, was neurologically unremarkable, with no evidence of atrophy, areflexia, or ataxia. The patient's father had died at 51 of arteriosclerotic heart disease and was not examined at that time. However, he had been in Veterans Administration hospitals frequently during the last ten years of his life for treatment of heart disease. Review of his chart disclosed signed examinations by 13 physicians who noted normal posture and muscular development. At the examination just prior to his death, he was noted to have equal and active reflexes. This would seem sufficient evidence to conclude that he did not suffer from Charcot-Marie-Tooth disease. Some cerebral deficit may have been present, however, since it was the unanimous opinion of all members of the community and most of his family that he was a ne'er-do-well and an alcoholic. A photograph made just prior to his death suggested a right lower facial weakness. Examination of the father's four living siblings and the mother's five siblings revealed no evidence of Charcot-Marie-Tooth disease. It was evident from photographs and affirmed by the family that this disease did not exist in the only deceased fraternal sibling who died at the age of 65. The maternal grandmother, aged 74, showed no evidence of Charcot-Marie-Tooth disease but did have absent ankle jerks.

CASE HISTORIES

Case 1. (V, 2). An 18 year old white male was born precipitously at term after a normal pregnancy. He developed normally and was well until the age of six when he had a convulsion. He continued well until the age of eight when he developed seizures with varying focal, grand mal, and psychomotor features. He was a behavior problem in school prior to the onset of his seizures and after the development of these he was forced to leave school. In a photograph at the age of nine his hands had a "claw" character, but it wasn't until the age of ten that it was noted that his feet turned in and he developed a "hump" on his back. He was diagnosed by a neurologist at this time as having Friedreich's ataxia. His feet developed such a marked varus deformity that they had to be corrected surgically at the age of 15. His seizures were partially controlled with a combination of anticonvulsants. He has continued to show dissocial, irritable, and suspicious behavior and has been a trial to his family and to hospital personnel during his hospitalizations.

Examination revealed an extremely kyphoscoliotic young male ectomorph, whose heart, lungs, abdomen, and genitals were within normal limits. He was alert and clear though resistive, occasionally irrelevant, and of borderline intelligence. There was no speech disturbance. Considerable atrophy of the legs was evident, more so in the pretibial regions (figure 1). There was slight varus

Case 1. (V, 2)

deformity and hammertoes of the feet bilaterally, worse on the right. His hands showed moderate atrophy of the thenar and hypothenar eminences, with wasting of the interossei bilaterally. The hands at rest were always held in a position of moderate flexion. Muscle testing showed only about 30 per cent of normal strength in flexion of the feet and great toes, with inability to evert or extend the feet or dorsiflex the toes. There was only trace strength left in extension of his hand and fingers and in opposition of his thumb and fifth finger. There was slight strength in extension of his thumb and supination of his forearm. The remainder of the muscles were intact. Muscle tone was within normal limits. There were no fibrillations or fasciculations. There was a complete deep tendon areflexia. Abdominal reflexes were equal and active. No pathologic reflexes were present. Even with a foot-slap bilaterally, the patient walked easily and with an awkward grace. The Romberg was negative. Finger-to-finger and finger-to-nose tests were normal, but heel-to-knee testing showed a slight ataxia. Except in the hands and feet there was no dysdiadochokinesia. Check, rebound, and posture holding tests and skilled acts were well performed. There was no dysmetria, dysarthria, decomposition of movement, or nystagmus. Of neurologic interest was the fact that the patient played a harmonica and rode a bicycle well. Sensory examination showed loss of vibratory sense below the wrist and knees, with diminution to the olecranon and iliac crest bilaterally. There were no palpable nerves. There was anesthesia to the mid-calf area with hypesthesia to the knees, more so over the lateral aspect of the legs, and hypesthesia and hypalgesia of the hands, with a fading border at the wrist. There was hypalgesia to the mid-calf area, highest over the lateral aspects of the legs. Position sense was absent in the toes and distal phalanges of the fingers. Fundi and visual fields were within normal limits. Vision was 20-20 bilaterally. Pupils were round, regular, and equal and reacted to light, but poorly to accommodation. There was slight flattening and weakness of the right lower face. The remainder of the cranial nerves were intact.

Results of the laboratory examination were as follows: normal white cell count, hemoglobin, urinalysis, VDRL, and spinal fluid chemistries. The electroencephalogram showed a left frontotemporal spike focus. Psycholometric test revealed an I.Q. of 75, with a probable native endowment of 80. Roentgenograms of the skull and chest were negative. Dorsal spine films showed a very marked kyphoscolyosis to the left, with moderate osteoporosis of all the vertebrae.

Case 2. (V, 5). The patient's sister, aged 35, similarly affected, was born at term after a normal pregnancy. As a child she was weak, easily fatigued, "nervous," and afraid of people. At about the age of ten she began to develop a "hump" on her back. At the age of 14 she had a nervous breakdown. She did not finish grammar school until the age of 17 years. She is married now, has one son, aged 14, one daughter, aged 3, and was at the time of examination in the last trimester of pregnancy.

Examination now revealed an alert, cooperative, somewhat tense white female of low normal intelligence. She was an extreme ectomorph, with a marked dorsal kyphoscoliosis. There was a varus deformity of the feet, with associated "hammertoes" bilaterally. There was a flattening of her thenar eminences and wasting of the muscles over the pretibial areas bilaterally. Muscle tone was questionably diminished. There was a slight weakness on extension of the fingers and hands, with absent extension and inversion of the feet and toes. There were no fasciculations. There were no deep tendon reflexes, but abdominal reflexes were equal and active. There were no pathologic reflexes. Romberg test was positive. Finger-to-finger and finger-to-nose tests were normal, but the heel-to-knee test showed a slight ataxia. There was a slight dysdiadochokinesia of the hands and feet but no abnormal check, rebound, or posture-holding tests, dysmetria, decomposition of movement, dysarthria, or nystagmus. Except for moderate foot-slapping on walking, the gait was within normal limits. Sensory examination showed hypalgesia and hypesthesia to the knees bilaterally, highest for light touch and on the lateral surface of the legs. Vibratory sense was diminished to the knees bilaterally, and position sense was gone in the feet and toes and diminished at the knees. There were no palpable nerves. Fundi, vision, and visual fields were unimpaired. Pupils were round, regular, and equal and reacted to light but poorly to accommodation. There were bilateral corneal reflexes and facial sensation was present. There was slight right lower facial paresis. Remainder of the cranial nerves were within normal limits.

Case 3. (V, 6). The third patient, a 21 year old married sister, born normally at term, did not walk until the age of three and was unable to climb stairs until the age of five. She was a good student, however, and not troubled by personality problems. At the time of examination she had just delivered a normal child after a rather stormy pregnancy and was just able to stand.

Examination revealed an alert, personable, extremely shy and frail person of average intelligence. She was unwilling to undergo a complete examination. There was a moderate kyphoscoliosis and moderate varus deformity of the feet bilaterally. No thenar, hypothenar, or interossei wasting was evident. In addition to the marked diffuse weakness of the lower extremities, she was unable to extend or evert her feet or extend her toes. There was slight to moderate equinovarus deformity, with hammer-toes bilaterally. Tone was diminished throughout. Deep tendon reflexes were absent throughout. Abdominal reflexes were not tested. Finger-to-finger, heel-to-knee, posture holding, and check and rebound tests were within normal limits. No dysmetria, dysarthria, dysdiado-

chokinesia, tremor, or nystagmus was present. Sensory examination revealed a hypalgesia and hypesthesia to the mid-calf region bilaterally, highest on the lateral aspect of the leg and to light touch. Position sense was gone in the toes and distal phalanges of the fingers and diminished at the ankles. Vibratory sense was gone below the acromian and patellar eminences bilaterally. There were no palpable nerves. Fundi and visual fields were within normal limits. Sight was excellent. Pupils were round, regular, and equal and reacted to light but poorly to accommodation. There were facial sensation and corneal reflexes bilaterally. There was a slight right lower facial paresis. The remainder of the cranial nerves were intact.

DISCUSSION

Although vertebral deformities are frequent in spinocerebellar diseases, it is rare in Charcot-Marie-Tooth disease. It was noted to be present in only 11 of 353 cases[4–10] and in seven of the 95 pedigrees in Bell's[3] large series. The presence of consanguinity was not mentioned in six of these seven pedigrees and was present only in the pedigree of Steinthal.[5] Only Guillian[11] has mentioned spina bifida in Charcot-Marie-Tooth disease. However, in Friedreich's ataxia, it is as important as the ataxia.[12] In cases of Roussy-Levy syndrome,[13-15] it was found in eight of 21 cases. DeBruyn and Stern,[16] in their review of hypertrophic interstitial neuritis, considered kyphoscoliosis a diagnostic feature.

Kyphoscoliosis was present in the cases of mixed Charcot-Marie-Tooth disease and Friedreich's ataxia, as reported by Van Bogaert and Moreau.[17] Spillane[18] and Roth[19] used this, plus other minimal neurologic signs, in their equivocal cases of Friedreich's ataxia in finding a transition stage between this disease and Charcot-Marie-Tooth disease.

In arriving at a final diagnosis here, the lack of a steady progression, incoordination, nystagmus, and so on prohibited a diagnosis of Friedreich's ataxia, the lack of progression and palpable nerves did not support hypertrophic interstitial neuritis, and the presence of atrophy and sensory changes was against a diagnosis of the Roussy-Levy syndrome.

In studying this family a few points of importance emerged. First was the finding in Charcot-Marie-Tooth disease of vertebral deformities, epilepsy, and mental and personality defects. The vertebral deformities were of special interest.

Since the maternal grandmother had a "hump on her back" and the defect was manifested in different siblings in both fetal and prepubertal life, and since roentgenograms of the spine showed generalized osteoporosis, the deformities would seem to be due to a genetic defect that resulted in faulty bone growth and metabolism. This is in contrast to the kyphoscoliosis in Friedreich's ataxia where the deformity is presumed due to a muscle imbalance and generalized osteoporosis is not present, a differential diagnostic point.

The rarity of these deformities in Charcot-Marie-Tooth disease and in this family, plus the fact that the nervous system develops from ectoderm and the vertebrae from mesoderm, would indicate at least two different genetic processes were at work in these cases. Studies in the field of chemical genetics suggesting "a gene for each enzyme" support this idea.

The relationship of these cases to the radiologic disease, kyphosis dorsalis juvenilis,[20] in which familial cases occur, is interesting because of the minimal and abortive forms of Charcot-Marie-Tooth disease that occur and the vertebral deformities in these cases that seem to be genetically transmitted. Three such possible cases were encountered by the author while gathering data on the family in this study. The phenomenon of translocation of genes might be a factor in this association.

The definite ectomorphism in this sibling group, whose parents and ancestors were of dominantly mesomorph body type, as well as the right lower facial flattening and impairment with convergence would seem to be associated with the genetic background of two consanguine marriages in the immediate forebears. Two epileptics, one congenital heart disease, one imperforate anus, and perhaps one death at 28 due to an enlarged heart also seem to be marks of this consanguinity. The "B" branch of the pedigree has not suffered from these defects.

SUMMARY

1. A sibling group with three cases of marked kyphoscoliosis in Charcot-Marie-Tooth disease, a case of spina bifida, a case with imperforate anus, and a case of congenital heart disease, products of a dominant inheritance pattern and consanguinity and part of a gene-

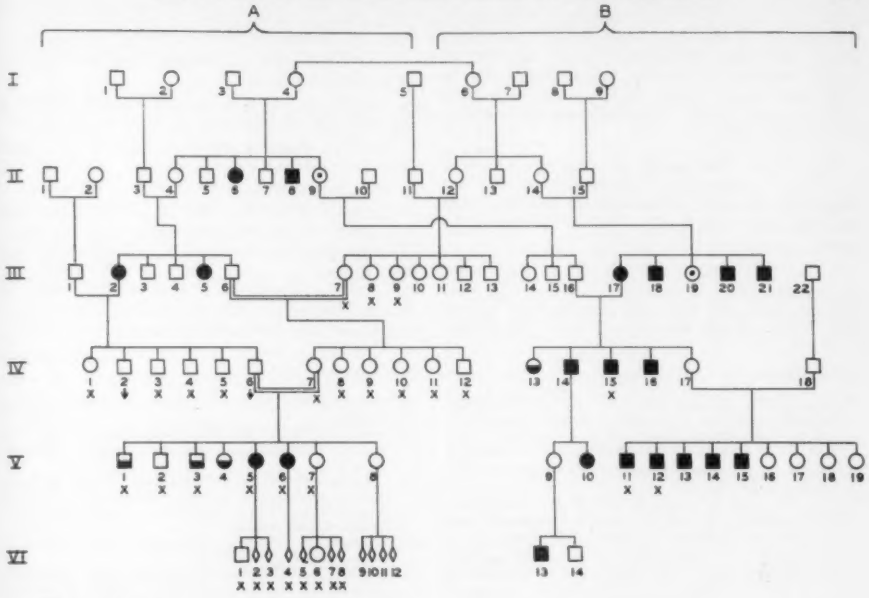

FIG. 2. Genealogical chart of family affected by Charcot-Marie-Tooth disease.

alogy of Charcot-Marie-Tooth disease through six generations, is presented here.

2. Thirty-one members of this group were examined by the author. Information on 24 affected members is presented.

3. The vertebral deformities plus osteoporosis in these cases are shown to be due probably to developmental defects of genetic origin.

4. Other hereditary spinocerebellar diseases in which vertebral deformities are found are discussed.

5. A possible relationship between this condition and kyphosis dorsalis juvenilis is noted.

6. The appearance of ectomorphism from a family of mesomorphs in which consanguinity was prominent is noted.

APPENDIX

Clinical data concerning the affected members shown in the genealogic chart (figure 2) is presented below.

Case (V, 11). This patient was an alert, clear, cooperative, 60 year old successful farmer who told of his disease beginning around the age of 13 and progressing slowly until about age 35. At the time of examination, he stood erect and was able to engage in hard physical work. Neurologic examination revealed bilateral "claw" hands, pretibial atrophy, hammer-toes, and moderate varus deformities. There was only slight strength in extension of his hands and fingers and opposition of his thumb and fifth finger. He was unable to extend or evert his foot or toes. He walked with a foot-slapping gait bilaterally. There were no fasciculations. Results of coordination testing were unremarkable. There was hypalgesia and hypesthesia of the feet, with loss of position sense in the toes. Vibratory sense was gone below the knees and diminished in his hands. Examination of the cranial nerves was nonrevealing.

Case (V, 12). This patient would not permit an examination but, when seen at close range, he was obviously as severely affected as his brother.

Cases V, 10, 13, 14, and 15
Cases IV, 14, 15, and 16
Cases III, 17, 18, 20, and 21

Case (V, 11) told of these being affected the same as he. All were reported to have "creeping paralysis." This was confirmed by many of the townsmen. They all affirmed that the

disease was of varying severity in any one sibling group, with some having both hands and feet severely involved so that they were barely able to walk and others having only trouble with their feet to a mild degree. None had any obvious vertebral deformities.

Case (III, 2). This family member was described as a large woman of odd temperament who developed a "hump" on her back in her late teens and had high arches. She died at the age of 71 years.

Case (III, 5). This woman began to have trouble with her feet in her early thirties, with progression until she was "all crippled up" in the latter years of her life and unable to ambulate from her home. She died at the age of 65.

Case (II, 6). She had trouble with her feet and "they looked funny."

Case (II, 5). He was an alcoholic and walked on the sides of his feet with the toes turned in.

Cases (I, 4 and I, 6). Two sisters were apparently the precursors of this disease. Whether they or their forebears had this disease is unknown.

Cases (1, 3 and III, 22). These individuals had the same surname as did cases I, 1 and III, 1. Whether they were related is unknown, but this is mentioned as further evidence of consanguinity, since at the beginning of this pedigree only 12 families existed in this mountainous community, an area of over 800 square miles.

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■ The sneering expression, caused by the angles of the mouth being drawn backwards and upwards, and known as the risus sardonicus, in association with spread nostrils, staring and prominent eyes, knitting of the brows, and bristling of the hair, is so often present as to be properly reckoned as pathognomonic of tetanus. In the fits of spasm the lips are often drawn apart so as to expose the set teeth, but sometimes they are kept tightly pressed together by the spasmodic action of the orbicularis oris.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves,* published in 1871.

The narcolepsy syndrome

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THE FUNDAMENTAL MANIFESTATION of narcolepsy is a disturbance of the sleep cycle, usually with persistent drowsiness and periods of uncontrollable sleep. In addition, there may also be cataplexy, fugue-like episodes, sleep or relaxation paralysis, hypnagogic hallucinations, and other abnormalities of behavior. This review is based on a series of 128 patients examined and treated at the University of Michigan Hospital during the last 20 years. No opportunity for autopsy has arisen.

NARCOLEPSY

Patients with narcolepsy apparently suffer from a persistent though fluctuating impairment of wakefulness; when this is increased, there are episodes of profound drowsiness or sleep. The tendency for sleep fluctuates so that "there seems to be an irregular cycle of sleepy and wide awake days." Somnolence is often more marked in the afternoon. Many of the patients studied complained of ease of fatigue or of feeling tired all or most of the time. Sleep appeared on slight provocation and was irresistible or at least difficult to resist, independent of the amount of nocturnal sleep. Many patients went to sleep at every cessation of physical activity and were compelled by this disability to avoid types of employment in which there was not constant bodily movement. Some patients felt sleepy at all times and tried to alert themselves by drinking coffee, slapping their faces, or washing with cold water, but without effect. Others were not aware of their impairment of wakefulness and denied that they were sleepy, even when appearances belied this. Two patients had drowsiness waves recorded in their electroencephalograms while they denied being sleepy. It would appear that these patients had become acclimated to their impaired wakefulness.

In 94 per cent of cases episodes of sleep occurred at some time or another when the patient was physically active. On occasion this activity was an enjoyable one, such as dancing. Sleep came from no apparent cause at times and appeared at any time and under any circumstance, but all patients suffered from frequent episodes of sleep that were provoked by factors that bring on physiologic sleep. Relaxation was the most important of these factors, but monotony was also a frequent one. Interest helped some to stay awake for long intervals, but this could happen only when interest was real and active. These prolonged periods of wakefulness were then followed by increased sleep during the following few days. Warmth facilitated sleep considerably, but many patients objected more to damp than to warm weather. Sleep often came on while riding in an automobile, even when the patient was the driver. Many patients could not do much reading and could not watch television or movies because of a tendency to sleep. Repletion precipitated sleep so readily that many patients went to sleep while eating.

The onset of acute episodes varied in rapidity. Some patients drifted into sleep so quickly that they even denied having had a warning feeling. Most episodes of sleep, however, were preceded by drowsiness which patients were able to resist with great difficulty and often only for short intervals of time. Some patients were capable of aborting this drowsiness with physical exertion, but this effort resulted in unpleasant feelings, such as excessive tiredness or headache, for the rest of the day. The duration of sleep episodes varied from a few seconds to many hours, but most often lasted from ten to 20 minutes. Short episodes were apt to keep recurring during the day. Long episodes were more common when the patient was lying down comfortably and had no compulsion to stay awake. A few patients would sleep almost continually through

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a weekend, only getting up to eat and drink. Generally sleep was light. Many patients related that they could still hear what was said around them, even if sleep forced them to keep their eyes closed. Complete detachment from the surroundings was not common. All patients could be aroused readily from sleep. A few had to be shaken to be aroused, and others tended to return to sleep immediately afterward. As a rule, patients felt refreshed after these episodes of sleep, and some commented that they felt as much refreshed as by a night's rest. A few, however, stated that they were still drowsy on awakening or on being awakened.

Night sleep lasted from six to ten hours or more and was restful in the majority of patients. In about 12 per cent night sleep was disturbed at some time or another during the course of the narcolepsy. Patients then complained of restlessness at night, partial insomnia, and nightmares. Some were seen to jerk or to have muscular twitchings during night sleep. Episodes of somnambulism occurred in 3 per cent. On awakening in the morning patients were usually refreshed, but a few complained that they still felt drowsy. They could disperse this drowsiness with exertion.

In addition to episodes of actual sleep, 25 per cent had episodes of severe drowsiness during which they continued their usual activities. Patients committed more mistakes than usual when they stayed active during these episodes. Six patients had car accidents while driving and one of them died from the accident. During these episodes of drowsiness, some patients were noticed to have glazed eyes and a staring look. Perceptual awareness was reduced, vision was blurred, and hearing was dulled. One patient said that he was unable to focus his eyes at all and that sensation from all external stimuli seemed dulled and remote. These episodes of drowsiness were terminated by bumping into objects or being jolted and sometimes by a feeling of embarrassment when people laughed or made remarks about them.

It should not be taken for granted that drowsiness described by narcoleptic patients always has the same quality as normal sleepiness. One patient declared that the warning preceding his attacks of sleep "is not a true sleepy sensation," although he could not describe it differently. Apparently some patients use the term drowsiness for want of other terms which would describe more accurately what they feel. Some patients used other terms, such as "dopiness," "semistupor," or "bewilderment," or said that they "felt in a daze," or "were in a trance or a long way away." These feelings are probably feelings of unreality, as have been described in cases of sleep paralysis.[1]

FUGUE-LIKE EPISODES

Eight per cent of the patients at some time or another have had fugue-like episodes during which they continued to walk, drive, talk, work, and be active in many ways, but with complete amnesia for what they had done. During these episodes patients tended to commit more mistakes than they would have committed had they been alert. They spoke jargon and wrote illegible scribble, but they could continue to carry out well a project which they had decided upon before the attack. Thus, a patient who was driving along a winding road woke up suddenly parked at his home, not knowing how he had arrived there. These attacks were interrupted if the patient met with unexpected stimulation. The activity was always logical, coherent, and relevant to the time and the place in which it was accomplished. Encephalography on these patients did not show any signs of epilepsy, even when a localizing record with temporal leads was carried out.

CATAPLEXY

Episodes of sudden and transient loss of muscle tone with retention of consciousness occurred in 54 per cent of patients. In 94 per cent of these, cataplexy was at some time or another provoked by laughter, especially irresistible laughter. Those patients who were "ticklish" had an attack when tickled. Attacks were provoked also by anger, fear, surprise, excitement, or anything that produced a rapid surge of emotion. Fatigue apparently facilitated collapse. Some patients developed attacks mainly during the evening after a long day's work. A patient who became weak on climbing stairs at times would collapse at the top and roll back downstairs.

During severe attacks patients were "as limp as a dishrag." They collapsed to the ground and could not move or talk. Some could groan. A patient whose arm was burned during the paralysis could do nothing about it. Patients knew what was going on around them and were aware of their state of paralysis. Perceptual awareness was reduced in some patients and others complained of blurred vision preceding or following an attack. Many patients could not see because of ptosis. Diplopia preceded the attack in a few cases. One patient described what appeared to be oculogyral spasm which persisted throughout the attack.

The duration of attacks was short. As a rule they lasted from one to two minutes. Some patients arose immediately on touching the ground. Attacks apparently lasted until the patient was capable of controlling his emotions. They often could be interrupted at any moment by touching the patient. One patient who could predict her attacks from a "tightness" of her voice was able to shorten them by gripping herself tightly with both arms or by rubbing any part of her body.

Patients fell to the ground only on occasion. As a rule they had time to get to a chair or to catch at objects to avoid falling. In many cases attacks were so trivial as to be noticed only by the patients themselves. Loss of tone was always symmetric and might be characterized by dropping of the jaw, sinking of the head, or collapse of the arms; buckling of the knees was common. During attacks patients dropped objects which they happened to be holding in their hands. Muscle twitchings were observed in about 4 per cent; these were seen in the eyelids and face, but in one patient the arms and shoulders also jerked. Another 4 per cent also suffered from "shaking spells" which were characterized by tremor present while the patient was otherwise limp. These latter spells were also provoked by emotions such as sorrow, anger, and laughter.

SLEEP OR RELAXATION PARALYSIS

Nineteen per cent of the patients experienced episodes of paralysis when drowsing off into sleep or awakening from sleep but still drowsy. These attacks might be associated with diurnal as well as nocturnal sleep. The paralysis had the same clinical characteristics as cataplexy, but it lasted much longer, often for many hours unless interrupted. The paralysis could be terminated at any moment by touching or jerking the patient, but occasionally it would recur on drowsing off again unless the patient moved about actively. At times patients could interrupt their own attacks of paralysis by managing to roll out of bed and jerk themselves. Episodes of sleep or relaxation paralysis were often accompanied by dreamy states, hallucinations, or tense anxiety, but could occur without any of these associated symptoms. They occasionally came on with no relation to sleep, and one patient found it was necessary to sit on the edge of the chair to avoid relaxing, since he would become paralyzed otherwise.

MOMENTARY SPELLS

Spells of momentary duration were described by a few patients. One developed black-out spells lasting approximately a half second, during which he would drop objects which he might be holding in his hands. These spells had their onset many years after the onset of typical episodes of narcolepsy and cataplexy. There was no family history or other history of epilepsy; electroencephalography showed sleep activity as well as sharp and complex discharges at the left temporal and posterior head regions.

REDUCED PERCEPTUAL AWARENESS

In addition to the reduced perceptual awareness which occurred at times during episodes of drowsiness, some patients experienced isolated episodes of reduced perceptual awareness which affected one of the senses singly. Blurred vision was the commonest of these complaints. One patient complained of deafness which came in episodes lasting about 20 minutes each time. Another patient complained of loss of taste and smell, but no loss was found when he was tested. Several patients related that they felt numb to pain or touch. One complained that his legs and feet, from the knees downward, went to sleep as soon as he rested. Another felt that all her body went to sleep; she got up and touched objects around the room and was then suddenly aware again of the presence of her body. In all these

cases the disorder of perception was symmetric.

HALLUCINATIONS

Hallucinations occurred in at least 10 per cent of cases and were associated with night as well as with day drowsiness. They usually occurred while going to sleep and were often accompanied by sleep paralysis. The subject matter of these hallucinations was derived from experiences familiar to the patient and generally it was unpleasant. The images were simple and were so clear and vivid that patients entertained no doubts as to what they had experienced. One patient who experienced the hallucination of a dog sitting next to him believed the dog to have been unreal only because other people had never seen it.

All the senses have been disturbed by hallucinations. A few patients had more than one sense affected; they saw objects and heard voices. The descriptions given by various patients included "a metallic taste in the mouth," "odor of iron which is wet and of very offensive tin cans," "human hands clutching at various parts of the body," "the sound of persons walking downstairs," "faces of Japanese and Russians." Two patients felt that their bodies had grown larger than usual. One patient felt as though he were sliding to the floor and could feel himself on the floor, but when he woke up in a few minutes he was seated in the chair as he had been before. Visceral hallucinations also occurred. One patient complained of dull epigastric pain unrelated to anything and relieved by sleep; all tests for this pain were negative. Other patients had "hunger-like felings" or "a craving for food, particularly carbohydrate food" occurring during episodes of drowsiness; there were none of the other symptoms associated with hypoglycemia and all laboratory tests for blood sugar disorders were negative.

TENSE ANXIETY AND OTHER SYMPTOMS

Several patients suffered from episodes of tense anxiety which generally accompanied episodes of sleep paralysis or hallucinations. This anxiety, however, appears to have been in excess of what one would expect in patients who had already been through these experiences many times. One patient explained that she knew all the time that she had no cause for alarm but she had no control over her emotions while drowsy. Another patient, who did not suffer from hallucinations and was not alarmed by his paralysis, was worried by ideas about spiritism; he explained that he had no control over these ideas during states of drowsiness and that he was frightened because of them. These emotions were accompanied by such manifestations of disturbed autonomic system as usually accompany anxiety. However, palpitations of the heart, deep respirations, vasomotor disturbances, profuse sweating, and the like have also occurred independent of emotion. They preceded, accompanied, or followed episodes of sleep or paralysis.

Pain was common, and patients complained of dull, midline ache, vaguely localized and regional in distribution. This ache was generally referred to the spine or head. Headache was dull, vague in localization, and bilateral. It was characterized by a feeling of heaviness, tightness, pressure, or tension at the head or neck. At times headache was referred to the region of the eyes. Vomiting was not rare, and on occasion patients spoke of sick headaches which were described vaguely. All these unpleasant feelings were exacerbated when the patient resisted sleep or was not allowed to sleep.

MENTAL SYMPTOMS

Difficulty with concentration was a frequent complaint. Some patients appear to have been suffering from a state of persistent distraction; however, this could be overcome by interest or by effort. Patients missed questions put to them, lost the trend of conversation, omitted words while talking, and had periods of forgetfulness. Some complained of slow thinking and inability to make quick decisions. Several lacked initiative and were apathetic. Other patients persisted in their activities, but performance was slow and achievement declined; yet the intelligence quotient was generally elevated and thought was logical and coherent. Depression of mood was common, but emotional instability was rare. One patient who had fits of crying lasting up to an hour said that crying was not accompanied by despondency or depression; it relieved her. A few patients suffered from obsession of ideas. Some

presented problems of behavior, but usually there was no personality disintegration. Five patients developed paranoid psychotic states on the basis of their hallucinations.

DIPLOPIA

Episodes of diplopia occurred in 5 per cent of cases. This preceded or followed episodes of cataplexy or sleep. In one case diplopia occurred only when episodes of narcolepsy were provoked by reading and on no other occasion. In another patient diplopia preceded episodes of sleep or paralysis by several years.

PHYSICAL AND NEUROLOGIC EXAMINATION

Examinations showed no objective abnormalities except for the following: 1) Obesity was present in about 20 per cent of cases. Many dated the onset of their obesity from the date of onset of their narcolepsy. The type of obesity was not typical of any recognized endocrine disorder. Only 3.2 per cent of the cases gave a family history of obesity. 2) A low basal metabolic rate, less than minus 13, was present in 45.5 per cent of the 70 cases in whom the rate was measured. In some patients the rate was very low, but the clinical picture was not one of thyroid dysfunction. There were no changes in the skin, hair, hair distribution, subcutaneous tissue, or voice; blood cholesterol, protein-bound plasma iodine, and inorganic plasma iodine were within normal limits; thyroid medication raised the metabolic rate in some cases but did not improve the narcolepsy. 3) Nystagmus (six cases), anisocoria (five cases), and unilateral ptosis (two cases) were also observed.

Lumbar puncture, when performed, showed no essential abnormality of cerebrospinal fluid pressure or composition of fluid. Roentgenograms of the skull and chest were essentially normal. Other investigations included hematologic studies, fasting blood sugar levels, glucose tolerance tests, blood calcium and phosphorus estimations, and serology; all were found to be within normal limits.

ELECTROENCEPHALOGRAPHY

Only the findings of patients who have had electroencephalography within the last ten years are reported here. There were 40 such patients. All their recordings show evidence of drowsiness at some time during the study. In five cases this drowsiness was minimal, but was marked in the others. In nine cases evidence of drowsiness was almost continuous. Sleep spindles appeared in only three cases. Waking rhythm was definitely normal in 27 cases. In many cases there were periods of slight dysrhythmia; however, this was not characteristic and perhaps not even marked enough to consider the recording outside normal limits. Waking rhythm was abnormal in two cases. One of these has been mentioned above; the other showed deep level, abortive, paroxysmal discharges with some resemblance to epilepsy.

COURSE AND TREATMENT

As a rule the disease took some months or years to develop to its maximal intensity. Remissions were not rare, particularly at the onset of the disease. Relapses at times followed periods of overactivity or unusually prolonged wakefulness. Paralytic episodes generally started some time after narcolepsy had been established, but in a few cases cataplexy was the first or an early symptom. Cataplexy disappeared completely in many cases after periods of time which varied from a few months to many years. Narcolepsy has persisted in all patients but one, who had suffered only from persistent somnolence which responded to amphetamine. In some cases narcolepsy has been present for over 40 years. However, there seems to have been a definite tendency toward improvement with time, an impression gained by questioning 21 persons who had suffered from narcolepsy for more than ten years. Only 29 per cent of the patients stated that there had been no improvement. Some of the others, though still subject to their disability, were leading practically normal lives, usually with the help of drugs.

Of the many drugs that were tried, good results were obtained from amphetamine sulfate (Benzedrine), dextro-amphetamine sulfate (Dexedrine), metamphetamine hydrochloride (Desoxyn), and occasionally ephedrine. These drugs relieved narcolepsy in 75 per cent of cases on whom a follow-up of some sort was done. Cataplexy and sleep paralysis and its associated symptoms were also relieved to some extent. The effect on cataplexy was not

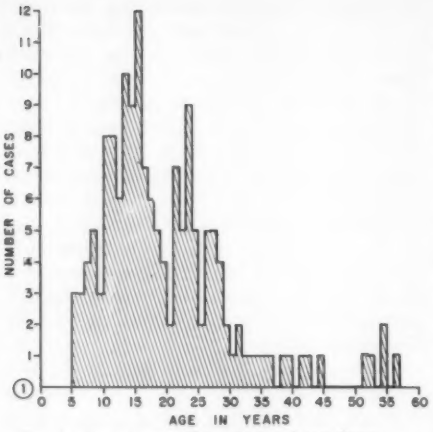

FIG. 1. Age at onset of symptoms of narcolepsy.

so manifest as on narcolepsy, but attacks of cataplexy were generally made less frequent and less severe by drugs. Daly and Yoss[2] recently reported very favorably on methylphenylpiperalacetate hydrochloride (Ritalin), which also gave them good results in relief of cataplexy, and Aird[3] has described favorable response to cataplexy with phenacemide (Phenurone).

ETIOLOGY

In this series 59.6 per cent were males and 40.5 per cent were females. Male preponderance was also reported by Daniels.[4] The age at onset of symptoms is charted in figure 1. In 80 per cent the onset was before the age of 30, and in 46.2 per cent the symptoms were first noted between the ages of ten and 20 years. A family history of epilepsy was obtained in 3.2 per cent of cases, and another 3.2 per cent gave a history of increased tendency to sleep in some member of the family. A doubtful history of epilepsy associated with narcolepsy and cataplexy was obtained in one patient; two had had childhood convulsions.

In 18 per cent of patients there was either a personal history of infection with delirium or of narcoleptic symptoms a few weeks or months after a nonspecific infection. At times, however, there was a long interval between a severe infectious illness and the clinical appearance of narcolepsy. History of trauma to the head followed by unconsciousness was obtained in 4 per cent. One patient dated the onset of symptoms from a period of overexertion at age 42 when he went without sleep for several days. Similar occurrences have been reported by others.[4]

DISCUSSION

The first description of a case manifesting the syndrome later known as narcolepsy was that of Westphal[5] in 1844, but the term narcolepsy was first proposed by Gelineau[6] in 1880. The case described by the latter author also had episodes of cataplexy, but the importance of these features was not appreciated until Löwenfeld[7] drew attention to them some years later. Sleep paralysis was first described by Mitchell[8] under the term "night paralysis," but Levin[9] later recognized that paralysis could also occur with diurnal sleep. The association of sleep paralysis with hallucinations was reported by Moyer,[10] with dreamy states by Münzer,[1] and with feelings of tense anxiety by Rosenthal.[11] Brain[12] included episodes of somnambulism with the narcolepsy syndrome.

Evidence has accumulated suggesting that the disturbance causing narcolepsy syndrome has a subcortical origin. Foerster[13] recognized the importance of subcortical lesions in the production of disturbances of consciousness, and von Economo[14] drew attention to them in disorders of sleep. Jefferson,[15] Cairns,[16] and others demonstrated definite correlation between clinical disturbances of consciousness and lesions of the midbrain and diencephalon.

Somnolence has been produced in experimental animals with lesions of the hypothalamus and subthalamus.[17–19] Moruzzi and Magoun[20] demonstrated electrocortical signs of arousal by electrical stimulation of the reticular formation, and Lindsley and co-workers[21,22] showed that the effects of stimulation were blocked by acute lesions to the basal diencephalon and tegmentum of the midbrain. Chronic lesions in the same area produced somnolence as well as electroencehalographic activity like that of sleep. This activity could be blocked only temporarily by afferent stimuli. Magoun evolved the concept of an ascending activating system which relays through multisynaptic pathways in the reticular formation to produce arousal and sustain wakefulness.[23]

Arousal and wakefulness may be maintained by impulses reaching the reticular formation by way of medial collaterals from the main sensory pathways.[24,25] Magoun demonstrated that somatic and auditory stimuli are capable of arousing the sleeping animal, even when the somatic and auditory afferent paths are interrupted bilaterally.[23] Thus it would appear that the rostral part of the reticular formation plays an important part in wakefulness and this is independent of other functions attributed to this area.

Somnolence has been produced also with experimental bilateral destruction of the amygdala.[26,27] Experimental studies of various observers have indicated that the hippocampus and the amygdala, particularly its basolateral portion are centers for emotional activities. These centers discharge by direct and indirect pathways into the tegmentum of the midbrain.[28] It would appear that the influence which the hippocampus and amygdala have over wakefulness is exerted through subcortical connections.

Judging from the effects of amphetamine on the arousal responses of experimental animals, it seems probable that this drug acts only at subcortical levels. It has been shown that the behavioral and electrical effects of arousal from amphetamine are apparently dependent on intact mesencephalic connections.[29,30] Amphetamine given to *encéphale isolé* preparations is still capable of alerting the cat to behavioral and electrical activity, but when the preparation is transformed to *cerveau isolé* by midbrain transection, the effect of the previously injected amphetamine is lost and the spindle and slow electrical waves that reappear cannot be influenced by amphetamine, even in high doses.[31]

Given to patients in proper doses, amphetamine sustains alertness, increases the power to concentrate and maintain concentration, and stimulates and prolongs the initiative to perform. Therefore, it seems justified to conclude that narcoleptic patients are disturbed at subcortical levels when they suffer from somnolence, inability to concentrate, lack of initiative, and fatigability, all symptoms which are relieved by amphetamine. Moreover, intravenous amphetamine is capable of producing immediate behavioral and electrical arousal during the episodes of drowsiness or sleep of narcoleptic patients.

The fugue-like episodes of narcolepsy differ from epileptic automatisms both clinically and electroencephalographically, but, because of their similarity in certain respects, the concept of the centrencephalic system postulated by Penfield[32] to explain the automatisms of epilepsy should be applicable also to those of narcolepsy. Using this concept, automatisms can result from dysfunction of the mesencephalic or diencephalic components of the centrencephalic system. Whitty[33] has described a case in which fugue-like episodes were apparently produced by microscopic lesions of the diencephalon.

Episodes of autonomic instability, craving for food, diplopia or oculogyral spasm, and abnormalities such as nystagmus, ptosis, and anisocoria that are found on occasion in narcoleptic patients are also indicative of a subcortical disturbance. The same consideration holds for the high incidence of obesity and of low metabolism levels without signs of thyroid dysfunction.

Wilson expressed the belief that narcolepsy is a form of epilepsy.[34] This view has of late been defended by Symonds, particularly with reference to cataplexy.[35] Electroencephalograms made on narcoleptic patients have been interpreted differently by different authors. The few recordings made during episodes of cataplexy or of sleep paralysis have been reported as not showing signs of epilepsy.[2,36,37] Recordings made during episodes of drowsiness or sleep show only a sleep type of electrical activity. Recordings made during waking periods have only rarely shown paroxysmal discharges of grand or petit mal type.[38] Almost all recordings show waking periods with a normal rhythm, but there have been occasional reports of a noncharacteristic dysrhythmia which has been interpreted by some as evidence of an epileptic disorder at a deep level.[39,40] Electroencephalographic studies with no evidence of epilepsy, even with activation, have been reported.[36,37,41–43]

Evidence to show that narcolepsy is not basically related to the epileptiform disorder can be summarized as follows: 1) narcoleptic patients derive most benefit from stimulant drugs, 2) episodes of the narcolepsy can be

interrupted readily and at any moment with stimulation, 3) episodes of drowsiness or sleep are generally provoked by the same agents that provoke physiologic sleep, 4) clinical analysis of cases indicates that narcoleptic patients suffer from a persistent though fluctuating impairment of wakefulness, and 5) electroencephalographic examinations suggest that narcoleptic patients are continuously verging on sleep. The sleep type of electrical activity that appears with drowsiness or sleep disappears following the injection of stimulant drugs.

The fundamental disturbance in narcolepsy is a depression of the mechanism concerned with wakefulness. This depression causes sleep which is abnormal for several reasons. It is irresistible and provoked easily under any circumstance, even when the patient has no cause for being fatigued. It generally is not a reproduction of the physiologic process of sleep. Complete detachment from the surroundings is uncommon. The spindle stage of sleep activity is seldom reached at electroencephalography. Furthermore, the drowsiness is often accompanied by dreamy states, hallucinations, automatism, tense anxiety, autonomic instability, or paralysis. It would appear that in these episodes there is not only a disturbance of the mechanism of sleep, but also of impulses which have synaptic connections at the tegmentum.

The cataplectic episodes of narcoleptic patients are provoked by emotional crises. Reference has already been made to the role played by the hippocampus and amygdala in emotion and to the connections of these centers down to the tegmentum of the midbrain. Laughter has close connections with the diencephalon. Foerster and Gagel[44] operated on a patient with a papilloma of the choroid plexus of the third ventricle and were able to provoke outbursts of laughter each time that they swabbed the blood from the floor of the ventricle. Druckman and Chao[45] contributed clinical evidence to show that the mechanical act of laughter is regulated by the diencephalon, and described a case in which episodes of forced laughter were associated with episodes of head nodding or of head dropping. Kelly[46] reviewed 29 patients with colloid cysts of the third ventricle, in six of whom there occurred attacks of sudden transient loss of muscle tone without loss of consciousness. Inhibition of muscle tone has been demonstrated with stimulation of the bulbar reticular formation.[47–49] Paskind[50] reported decrease of muscle tone in normal individuals during laughter. Decrease of muscle tone is a common experience during crises of fear, surprise, sorrow, and excitement and is at times accompanied by tremor. It would appear that decrease of muscle tone with or without tremor is a physiologic response during emotional crises until this loss is counteracted by other reactions. When the activating system is impaired in its functions, as occurs in narcoleptic patients, the descending reticulospinal facilitatory influences might be also impaired, with the result that emotional crises might provoke exaggerated loss of muscle tone until the patient is capable of controlling his emotion. Because this loss of muscle tone would be provoked by an agent that does not aggravate the impairment of wakefulness, no drowsiness would follow and there would be no electroencephalographic evidence of drowsiness.

Sleep paralysis is provoked predominantly by relaxation, which aggravates the impairment of wakefulness. With this aggravation the patient experiences not only drowsiness and paralysis, but also dreamy states, hallucinations, and tense anxiety, all manifestations which depend on impulses that have synaptic connections at the tegmentum. Sleep paralysis lasts much longer than cataplexy and is interrupted by somatic stimulation which breaks the vicious circle of relaxation causing paralysis.

It is difficult to say how the depression of wakefulness is brought about, especially since there is no material for histologic study, but one is tempted to speculate that the depression is secondary to a disturbance of some neurohumoral mechanism. This is suggested by the incidence of frequent, acute, short episodes of aggravation with rapid recovery, and particularly by the immediate recovery obtained with intravenous amphetamine. The improvement of patients with adrenergic drugs is worthy of special note, especially if one links this with the findings of Vogt,[51] who by a number of biological and chemical tests was able to identify an admixture of noradrena-

line and adrenaline in the central nervous system of cat, and to show that the concentration of noradrenaline in certain parts of the diencephalon or brainstem is at least six times its concentration in any other part of the central nervous system that was examined. Furthermore, the change in concentration of noradrenaline with injection of drugs suggests a specialized functional role for it at brainstem levels, in addition to its role as a synaptic transmitter at centers of sympathetic control. Experimental studies have shown that injected adrenaline, as well as adrenaline that is set free in the blood by stimulation of the splanchnic nerves or by other means, exerts direct influence on the ascending reticular activating system and on the descending reticulospinal facilitatory systems.[52,53] Dell reviewed this evidence and suggested the existence of a mechanism of adrenergic transmission at the level of the reticular systems.[54] Bradley and Elkes,[31] after a detailed study on the effects of certain drugs on the electrical activity of the brain, suggested that a slight variation in local titer of a neurohumoral agent in the key midline areas of the reticular formation may profoundly affect the excitability of large neuron pools at a distance; they expressed the belief that changes in function might depend on the rate of liberation, diffusion, and destruction of locally produced neurohumoral agents.

SUMMARY

A series of 158 cases with narcolepsy has been reviewed.

Evidence is strongly suggestive that the narcolepsy syndrome is a nonepileptic disturbance of subcortical origin. It appears to be a state of depression of the arousal system, possibly from a neurohumoral deficiency.

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■ It was long ago said that division of labour, or, more generally, differentiation, is a universal law. Things become increasingly numerous and more different, or, in other words, more complex. Differentiation is well seen in the development of animal organisms, and is seen, too, in the social organism. It would be very remarkable if there were an exception in the case of one part of the social organism, the body medical—if in so great a field of work as the medical there did not arise more and more different workers in different parts of that field. There is no exception. The body medical is now very complex; there are alienist physicians, neurologists, obstetric physicians, ophthalmic surgeons, aural surgeons, dentists, physiologists, chemists, etc.; the specialty of each comes out of, is differentiated part of, a wide general knowledge.

J. Hughlings Jackson in *Ophthalmology and Diseases of the Nervous System*, published in 1886.

Subcutaneous hemorrhages in multiple sclerosis

Roy L. Swank, M.D.

THE PURPOSE of this paper is to direct attention to a clinical phenomenon observed frequently in patients with multiple sclerosis. In 48 of 62 female patients who were observed repeatedly over five to nine years in Montreal, small subcutaneous hemorrhages were observed. In 32 patients the hemorrhages were spontaneous. In another 25 patients subcutaneous hemorrhages were not mentioned in the record and it can be assumed that hemorrhages were not observed in many of these cases. The present writer sometimes observed hemorrhages in patients who had not previously been aware of their presence. They occur on the extremities, usually legs or thighs. In those instances where their development was observed from the beginning, they appeared first as very small red spots several millimeters in diameter. In the course of 24 hours these spots spread out to become approximately 1 to 2 cm. in diameter and became a blue color. In another day or so they became yellowish and then gradually disappeared. Biopsies of five spontaneous hemorrhages, where trauma could be confidently ruled out, revealed extravasated red blood cells infiltrating the deeper layers of the derma and subcutaneous fat. There was nothing to distinguish these small hemorrhages histologically from extravasation occurring after trauma, spontaneous hemorrhage, or the small petechial hemorrhages which result from embolism. The blood vessels in these areas had a normal appearance. These hemorrhages have also been observed in male patients, but much less frequently, presumably because their skin is thicker and more darkly pigmented; thus the hemorrhages are obscured.

In addition to the small subcutaneous hemorrhages, the author also observed the spontaneous appearance of white linear streaks of the lower extremities in several patients. These appeared abruptly, lasted a few seconds, and then disappeared. The author has observed and a number of patients have described petechial hemorrhages in large number after having their blood pressure taken both under and distal to the blood pressure cuff, and petechial hemorrhages have been seen around the waist or at other places where constriction of the body by a belt or elastic had been present. This phenomenon is similar to the subcutaneous hemorrhages described by Shulman and co-workers[1] in capillary resistance studies.

These vascular phenomena (in particular the subcutaneous hemorrhages and white linear streaks on the extremities) appear periodically and frequently coincide with or precede activity of the disease as manifested by exacerbation of existing symptoms or the development of new symptoms. In the past six years during which these phenomena have been observed, they have become progressively less frequent as the disease itself has become less active (attacks less frequent) in our Montreal group of patients. Shulman and co-workers[1] also noted a correlation between changes in capillary fragility and clinical activity of multiple sclerosis.

One wonders why a manifestation as commonplace as subcutaneous hemorrhages has not been linked with multiple sclerosis previously. It is suggested that very careful and frequent observation of the same patients by the same observer over a long period of time is responsible, particularly for observation of the periodic "showers" of hemorrhages. No doubt hemorrhages have been observed before but were considered a complication of trauma. The patients reported in this paper bruised easily, but more important is the fact that the hemorrhages frequently appeared spontaneously.

The incidence of nontraumatic subcutaneous hemorrhages in normal individuals cannot be stated with any degree of accuracy. It appears

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to the author that their occurrence in multiple sclerosis is sufficiently frequent to merit some consideration in the pathogenesis of the disease. In preceding articles[2–7] evidence has been presented which implicates the vascular system and especially the blood itself in the pathogenesis of this disease. In the last few years there has developed increasing interest in the blood elements and clotting mechanisms in multiple sclerosis. Although it seems possible that the number of platelets[9] and concentration of fibrinogen[10] fluctuate and blood coagulability is decreased,[8] there are frequent contradictions[8] concerning these changes and the total picture regarding blood coagulation is obscure. In consideration of this matter, it is well to keep in mind that the course of the disease is characterized by remarkable fluctuation. Therefore, it is not unlikely that many of the changes accompanying the disease also fluctuate. This is indicated by a number of studies.[1,5,9]

The observations reported in this paper lend some support, although indirect, to the contention that multiple sclerosis is not localized primarily in or confined to the central nervous system.

SUMMARY

Frequent and periodic occurrence of small spontaneous subcutaneous hemorrhages in multiple sclerosis is reported.

I am indebted to Dr. E. Colton Meek, Jr. of the department of pathology, University of Oregon Medical School, for reviewing the histologic material.

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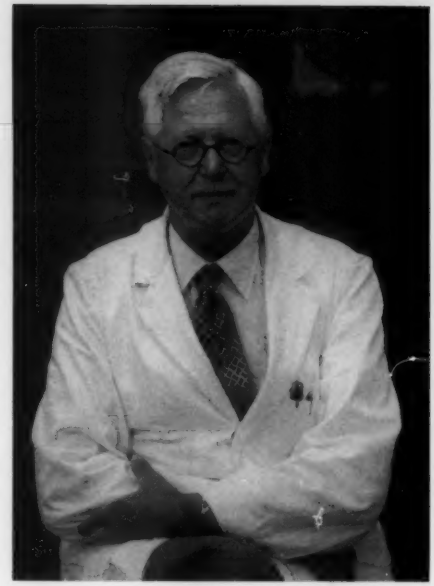
■ Inflammation of the membranes of the spinal cord is usually associated with inflammation of the substance of the cord (myelitis) or with inflammation of the membranes of the brain, but uncomplicated cases do occur now and then, and with care it is not difficult to discriminate between the symptoms which are essential to spinal meningitis and those which are only accidental.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

J. Godwin Greenfield

1884-1958



"TEACHER, PATHOLOGIST, AND FRIEND." With these words Sir Russell Brain described, far more adequately than can the present words, J. Godwin Greenfield, at the time he was honored by his University at Edinburgh in the past year.

Dr. J. Godwin Greenfield, M.D., F.R.C.P., L.L.D., died suddenly at Bethesda, Maryland, on March 2, 1958, still at the height of his productive contributions which have spanned more than 45 years. Dr. Godwin Greenfield returned to the National Hospital, Queen Square, after World War I to accept the first fulltime post of neuropathology ever offered by this world renowned institution. He functioned in this capacity until 1949, and even after retirement he continued research for another five years. During his last three years America was fortunate to have his wisdom and understanding during a part of each year, which he spent at the National Institute of Neurological Diseases and Blindness.

Although so disabled by arthritis that he had to use canes or crutches to ambulate, no word of complaint was ever heard in reference to himself. His productivity was high, and in the last ten years 16 major publications resulted from his research; two of these were monographs, and one culminated in the textbook which those interested in neurologic sciences have long anticipated. Dr. Greenfield was able to correct the proofs and index of his own textbook and thus to see it in print before his untimely death.

As a teacher, Dr. Greenfield held no peer. The literature in both English and European languages seemed to be filed inexhaustibly in his brain, and he was a continual source of information about any aspect of neuropathology. He always had time for the young man and his problems, and no problem seemed too naive or too demanding. He willingly shouldered even the personal problems of those of us who were his younger colleagues and our problems became his own.

Godwin Greenfield demonstrated a tremendous responsibility to his field. No matter how bad the weather or how icy the streets, he would not miss clinical rounds nor the pathologic discussions to which he had been invited. He fondly chose to call these sessions "Parade."

Godwin Greenfield would not tolerate unscientific observations. His articles were remarkable for their brevity, their clarity, their lack of speculation, and their pure observation. Such qualities have made them as valid today as when they were written. A recent example of this was the electroretinographic proof of his observations in the difference between infantile and juvenile amaurotic idiocy.

The halls of the National Institutes at Bethesda and the National Hospital in London will sound empty without the cheerful clatter of Godwin Greenfield's canes. Let us hope that the minds of neurologists, neuropathologists, and neurosurgeons, now and of the future, will not remain empty of the contributions Dr. J. Godwin Greenfield has left them as their heritage.

G. MILTON SHY, M.D.

CASE REPORT

Asian influenza virus as the cause of acute encephalitis

William E. Bell, M.D., A. P. McKee, M.D. and
R. A. Utterback, M.D.

As the Asian influenza virus infection spread across the United States in 1957, concern was expressed that significant disease of the central nervous system might be a complication. Presented here is the case history of a patient who suffered from Asian influenza virus infection, with acute encephalitis as the major manifestation.

A review of the literature in the era since viruses have been isolated reveals surprisingly little immunologic evidence for the widely held belief that the influenza viruses may produce acute encephalitis in man. This may be attributed partly to the extreme prevalence of influenza infection, with the result that agglutination titers may be demonstrated in many people any time a survey is made, thus diminishing the value of this indicator. The other major source of information is isolation and identification of the virus, a task which is difficult and easily subject to error. A good example of this approach and of the criticism that may be made is that of Broun.[1]

In the late spring of 1957 Asian influenza made its first appearance in Iowa. It seems almost certain that no immunity to this virus was present in our population prior to that time. Therefore, we feel there are two important implications in our identification of a case of this sort. First, it is significant that Asian influenza, thus far not implicated as the cause of nervous system disease, was demonstrated to act as a neurotropic virus. Second, and perhaps of even greater significance, is the very good evidence from the immunologic standpoint that an influenza virus can produce encephalitis.

CASE REPORT

A 62 year old white male railroad switchman was completely well until the development of the present illness. On August 7, 1957 he had a rapid onset of bitemporal headache. This symptom was accompanied by stiffness of the neck and shortly thereafter by vomiting. He was seen by his family physician who found a temperature of 102° F. Intramuscular penicillin was administered and symptomatic improvement followed. The patient felt much better the next day and, although mild headache still was present, he was able to return to work. However, on August 10 the headache and stiff neck recurred, along with photophobia, retro-orbital pain, and profuse diaphoresis. His temperature again was elevated to 102° F. He vomited frequently. The following day he was described as being "mentally confused and semicomatose." He remained in bed until his transfer to the State University of Iowa hospitals on August 13, 1957.

Physical findings. On admission the patient was acutely ill, with a rectal temperature of 102.4° F., blood pressure 138/70, and pulse 84 per minute. He was obviously more uncomfortable in bright light. Drowsiness was a prominent feature; although he could follow commands and answer questions, he frequently fell asleep while being questioned. The neck was mildly stiff. The pupils were 3 mm. in diameter and light responses were normal. The extraocular movements were full and without nystagmus. Examination of the fundi was normal; the optic disks were not elevated. The pharynx was mildly injected and petechiae were present over the hard palate. Chest, heart, and abdomen were not found to be abnormal. The sensory examination was intact to all modalities and the gross strength seemed normal in all limbs. He was hyporeflexic throughout. The responses to plantar stimulation were flexor bilaterally.

Laboratory studies. The specific gravity of the urine was 1.009; it contained albumin (1+), but no sugar. The microscopic examination revealed only an occasional white blood cell per high power microscope field.

The peripheral blood contained a hemoglobin of 12.6 gm., 4,240,000 red blood cells, and 10,200 white blood cells per cu. mm. A differential smear

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revealed 81 neutrophils, 10 lymphocytes, eight eosinophils, and one monocyte.

The blood serology was negative. Roentgenograms of the skull and chest were normal.

A lumbar puncture at the time of admission revealed an opening pressure of the spinal fluid of 160 mm. in the horizontal position. The fluid was slightly xanthochromic. The Pandy test was reported as positive (1+). There were 1,500 red blood cells, mostly crenated, in addition to 268 lymphocytes and 12 neutrophils per cu. mm. Quantitative analysis of the fluid revealed a protein value of 90 mg. per cent, glucose 79 mg. per cent, and chlorides 125 mEq./l. Stained smears of the spinal fluid revealed no organisms. The culture produced no growth. The agglutination test for brucellosis and the complement-fixation tests for Eastern and Western equine and St. Louis encephalitis, lymphocytic choriomeningitis, and mumps were negative.

Course. The patient was treated supportively with aspirin and alcohol sponges and given intravenous fluids for the first three days in the hospital. His temperature dropped rapidly to normal with this treatment and did not again go over 100° F. during his hospital stay. He vomited several times the first two days after admission. On the third day he began to improve in all respects; each day thereafter he showed gradual improvement. He became alert and oriented, and by August 18 (five days after admission and 11 days after the onset of the illness) he was asymptomatic. Another lumbar puncture on August 14 showed a persistent leukocytosis with 210 lymphocytes and 20 neutrophils; there were 160 red blood cells.

On August 22, shortly before discharge, blood was drawn for hemagglutination inhibition against Asian influenza virus and a titer of 1:6,400 was discovered. A blood specimen drawn on the day of admission nine days previously was titrated simultaneously and the agglutination titer was found to be 1:6,000 on this specimen. Thus, a four-fold increase in titer had occurred over a nine-day period. This is considered conclusive evidence that infection with the Asian virus had occurred and very strong evidence that this virus was responsible for the meningoencephalitis. The patient was discharged from the hospital on August 23 without symptoms.

DISCUSSION

In the wake of the influenza epidemic of 1918 to 1920 came a host of residual disorders of the nervous system. At approximately the same time as the influenza epidemic there was a worldwide epidemic of encephalitis — so called lethargic, or von Economo, encephalitis. The relationship, if any, between these two was never clearly understood. Virus studies were not then sufficiently advanced to permit either isolation of a virus or immunologic proof of infection. At the first meeting of the Association for Research in Nervous and Mental Diseases in December 1920, the discussion centered about epidemic encephalitis and the questions whether 1) the influenza virus and the encephalitis virus were two strains of the same organism (that is, one a mutant of the other), or 2) the virus of encephalitis and that of influenza happened only to coincide in time and age distribution in traveling from one country to another. The consensus, however, seemed to be that, although influenza might be responsible for nervous system symptoms, 1) typical cases of lethargic encephalitis were not associated with simultaneous occurrence of influenza in the same family, and 2) epidemiologists were not able to trace any definite path that epidemic encephalitis followed, although this was apparent for the influenza epidemic. In other words, they felt that two separate conditions were occurring coincidentally, virus encephalitis and influenza. Since that time there has been much speculation about influenza as a cause of encephalitis, but published reports have been inconclusive for various reasons.

A rather unique opportunity was presented with the Asian influenza epidemic, in that there was no reason to expect immunity in any of our people. An infection accompanied by an elevated and rising titer of immunity to Asian influenza virus at the onset of the epidemic would most likely be Asian influenza. This was paralleled, in our patient, by a typical acute meningoencephalitis. Indeed, the symptoms and signs were almost exclusively those of encephalitis. No residuals were apparent when he was last examined.

Judging from experience with previous influenza epidemics, the major significance of the present one may be in the pulmonary and central nervous system residuals. This seems already a possibility in view of the following quotation which came to our attention during the preparation of this report: "Twelve cases of encephalitis following influenza have been reported to CDC. None have been absolutely proved due to influenza, but most occurred during an epidemic. Three had CF titers above 1:128, and one had paired sera rise by HI test. They have occurred in various parts

of the country and do not seem related to equine encephalitis. Most are in teenagers and onset is about a week after onset of influenza. Five were fatal and the others have recovered after periods of coma, disorientation, or partial paralysis. One youth with a CF titer of over 1:128 was almost totally decerebrate for several days, but appears to be recovering."[2]

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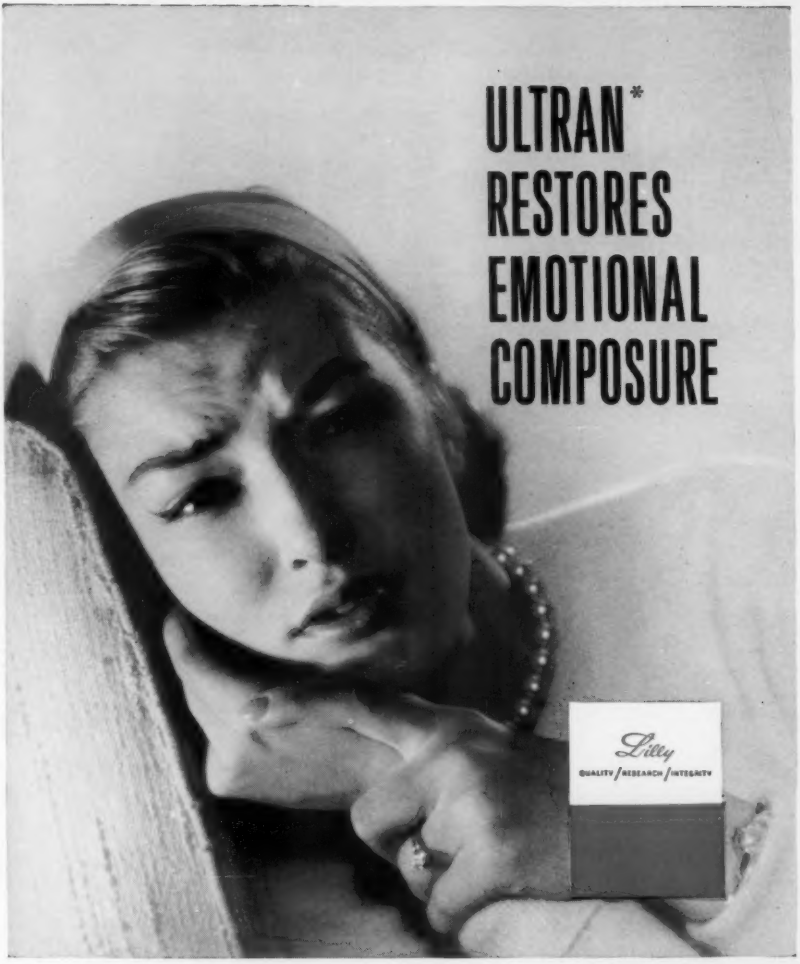
■ Epilepsy (I mean epilepsy proper) is nowadays considered by most medical men to be a disease of the brain. We should have two types of this morbid affection. I find, however, that many medical men have but one type—loss of consciousness with severe universal convulsion. But the great thing in the diagnosis of epilepsy is not the "quantity" of the symptomatology, but paroxysmalness. A sudden transitory loss of consciousness with very little physical manifestation, often enough suffices for the diagnosis of epilepsy. It may be said that there are "all degrees" of epileptic seizures, from slightest to severest. My experience is that a patient, long subject to *les petits-maux* only, has a very severe, perhaps a severest, fit some one unfortunate day, and afterwards is subject to them, and often to the slight fits too, without having fits of "all degrees." The two things, *les petits-maux* and *les grands-maux*, differ in compound degree; they deserve to be considered separately as types for diagnostic purposes. That epileptic fits are often very slight and transient is so very old a story that I will speak of one very important variety of *le* petit-mal to which very little attention has been paid. I must premise that loss of consciousness is not essential for the diagnosis of a slight fit of epilepsy; there may be defect of consciousness only.

J. Hughlings Jackson in *Remarks on the Diagnosis and Treatment of Diseases of the Brain*, published in 1888.



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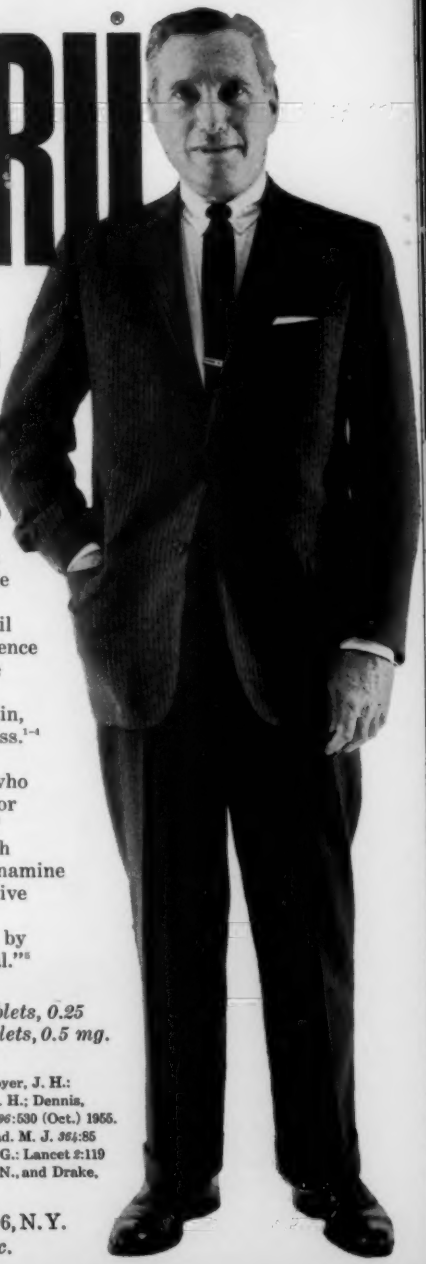

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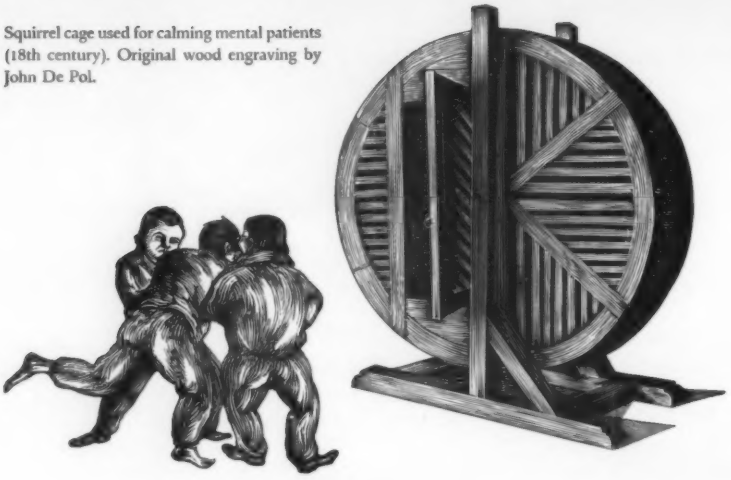

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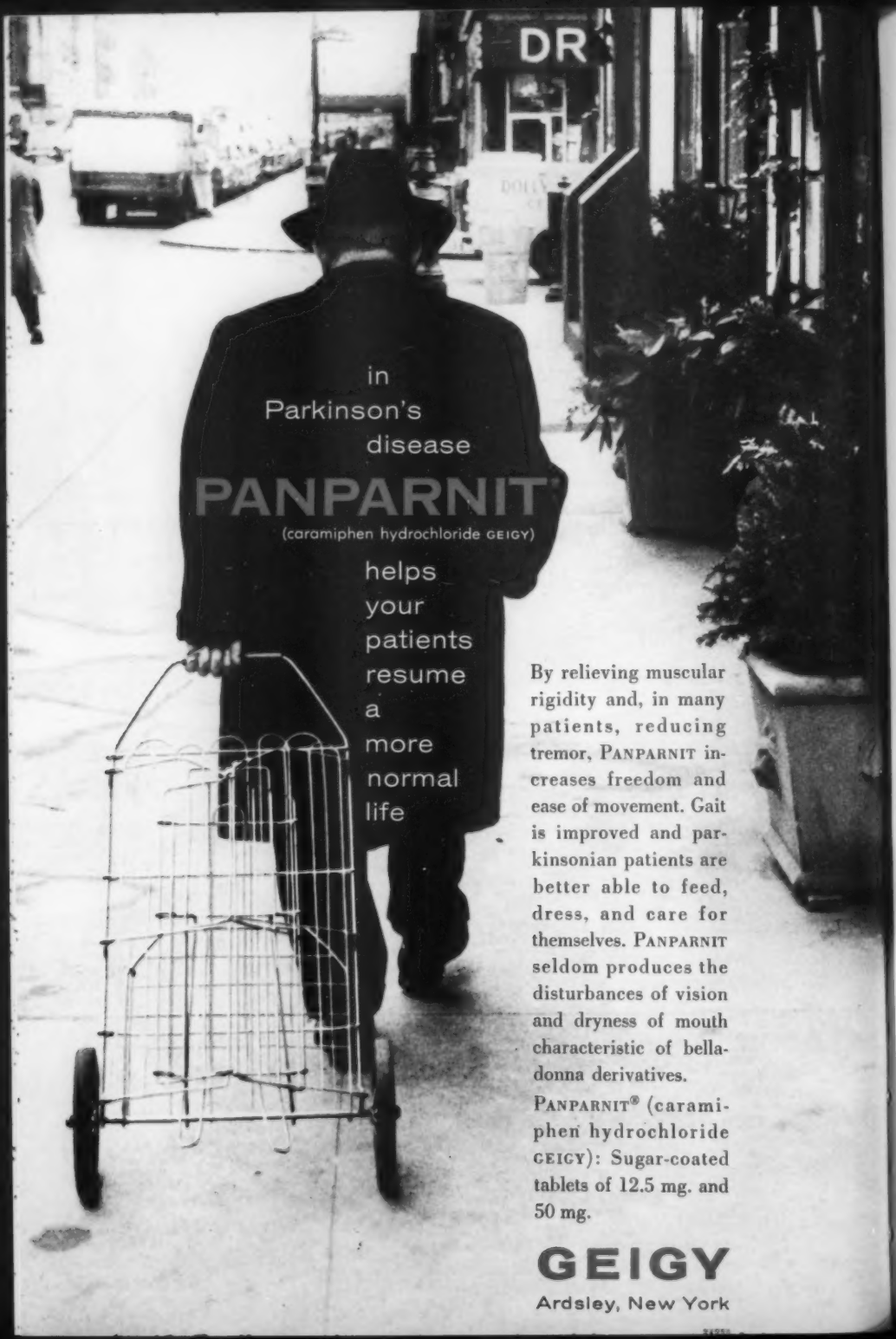

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JUNE 1958

Tenth Annual Meeting Marks Academy's Largest

The tenth annual meeting of the American Academy of Neurology held in Philadelphia's Bellevue-Stratford Hotel (April 21-27, 1958), shattered all previous meetings in attendance and activity records. Almost 900 AAN members registered for the meeting, and the attendance was further swelled by a goodly number of the Women's Auxiliary and guests. Enrollment in the special courses, which preceded the scientific sessions (April 21-23), also reached a new high. Three hundred and twenty-two individuals registered for the courses, which had a total attendance of 612, as follows: Neuropathology (47), Disorders of Movement (54), Neuropharmacology (68), Electroencephalography (76), Pediatric Neurology (76), Physiology and Diseases of Cerebral Circulation (54), Current Advances in Neurology (70), Neuro-Ophthalmology (80), and Fine Structure of the Nervous System (49), Course for General Practitioners (38)....Sixty-one presentations were made at the general scientific sessions and an additional 36 at the sessions of the special sections, making a total of 97 presentations. Moreover, there were on display 35 scientific exhibits, three society exhibits, five motion pictures, and 22 technical exhibits....The 1959 AAN meeting will be held in the Statler Hotel, Los Angeles (April 12-18). The 1960 meeting is planned for Miami (April 25-30).

AAN Sections Conduct Symposia

Special symposia featured the AAN section meetings in Philadelphia. The Section of Neurochemistry conducted a symposiom on the neurochemistry of amino acids (Eugene Roberts, moderator, and Guy McKhann, secretary), and still another symposium on the neurochemistry of nucleotides in joint session with the new Section of Neuropharmacology (Morris Friedkin, moderator, and Guy McKhann, secretary). The symposium of the newly formed Section of Neuroanatomical Sciences centered on discussions of the cerebellum, under the chairmanship of Roy S. Snider. In addition, this section presented 16 papers on miscellaneous topics. The new Section of Neuropharmacology held a symposium on the pharmacologic stimulation of the central nervous system, with J. E. P. Toman serving as chairman.

Section of Child Neurology Formed in Philadelphia

As an expression of the recent surge of research and interest from neurologists and pediatricians in the neurologic diseases of infancy and childhood, there was formed at the Philadelphia meeting a new AAN Section of Child Neurology. The

purpose of the section is to advance communication and work in this field within the framework of the Academy programs and in consonance with its function and missions in neurologic practice and research and in neurologic education and training. The first scientific session of this section will be held at the next annual AAN meeting in Los Angeles (April 12-18, 1959)....Until the section has its first meeting and elects officers, Pearce Bailey will act as chairman and Richard L. Masland as acting secretary.

Benson Wins Weir Mitchell Award

D. Frank Benson, a second-year resident in neurology at the San Francisco VA Hospital, received the annual S. Weir Mitchell Award of the American Academy of Neurology in Philadelphia Thursday, April 24. This award, named in honor of S. Weir Mitchell (1829-1914), the "father of neurology" in this country, provides an all-expense trip to the annual AAN meeting, a prize of $200, and an opportunity to present the winning dissertation at the opening of the Academy's scientific sessions. The subject of Benson's paper was, "A Long-Term Study of Patients with Ruptured Aneurysms of Arteries Supplying the Brain"....The Weir Mitchell Award is given each year by the Academy and the Women's Auxiliary to a younger member for outstanding research in neurology.... Information about the 1959 award may be obtained from Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minnesota.

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ANA to Meet in Atlantic City

The eighty-third annual meeting of the American Neurological Association will be held at the Claridge Hotel, Atlantic City (June 16-18, 1958), under the presidency of Israel S. Wechsler....Meeting at the same time and place as the ANA is the spring meeting of the Medical Advisory Board of the National Multiple Sclerosis Society (Thomas L. Willmon, medical and research director), on June 15, and the semi-annual meeting of the Myasthenia Gravis Foundation (David Grob, secretary) on June 17....An account of the ANA meeting and other related activities in Atlantic City will be given in the July issue of the NEWSLETTER.

Canadian Neurologists to Convene in Toronto

On June 12-15 the tenth annual meeting of the Canadian Neurological Society will be held at the Toronto General Hospital and at the Hospital for Sick Children. The current president and host for this meeting is E. H. Botterell of the University of Toronto. Among the guest speakers will be A. Earl Walker (Baltimore), J. Purdon Martin (London), and John W. Mason of the Walter Reed Army Institute of Research. The scientific program includes two symposia: one on "Problems of Cerebrospinal Fluid Circulation" and

the other on "Some Neuroendocrine Pituitary Considerations".... Further information may be obtained from Dr. J. L. Silversides, Secretary-Treasurer, The Canadian Neurological Society, Suite 321, Toronto Western Hospital, Toronto.

Argentine Neurological Society Holds its First National Reunion The Neurological Society of Argentina held its first national reunion in Buenos Aires, April 18-20, 1958. The scientific sessions covered a range of neurologic problems, especially as they relate to clinical, neuroanatomic, neurophysiologic, and medicolegal considerations. The officers of this society[1] are: Julio Aranovich, president; Gustavo F. Poch, vice-president; Ricardo Garrote, secretary; Manual Ojea, treasurer. The Secretariat of the Neurological Society of Argentina is: Coronel Diaz 2760, Buenos Aires, Argentina.

New American Board Diplomates As a result of the latest examinations of the American Board of Psychiatry and Neurology, held in San Francisco (March 17-19, 1958), 15 candidates were certified in neurology. The names of the new diplomates are: James N. Allen, Chapel Hill; T. M. Badgley, Washington; J. H. Chandler, Royal Oak, Michigan; Sherwood Davidson, Boston; P. E. Duffy, Syracuse; H. C. Fang, Los Angeles; A. M. Iannone, Minneapolis; L. L. Jacobs, Lynwood, California; J. A. Logothetis, Minneapolis; Fletcher McDowell, New York; Frank Morrell, Minneapolis; Erland Nelson, Minneapolis; Sidney Schulman, Chicago; C. K. Smith, Bethesda; and R. E. Yoss, Rochester, Minnesota.

Thudichum Honored at Bethesda A one-day session on the history and progress of neurochemistry was held at the National Institutes of Health (April 19, 1958) to pay tribute to Johan Ludwig Wilhelm Thudichum (1828-1901), the "father of neurochemistry." The meeting was held under the joint auspices of the Basic Research Program of the National Institute of Neurological Diseases and Blindness and the National Institute of Mental Health....The morning session, under the chairmanship of Dr. Harold E. Himwich, was devoted to dissertations on Thudichum -- the man, his inner life, and his genius as a gastronome, as well as a chemist. After greetings by Robert B. Livingston, the biographic data on Thudichum were presented by David L. Drabkin, who has recently written a biography on Thudichum, and Percival Bailey. The discussion was opened by Donald B. Tower....The afternoon session was devoted to the development of neurochemistry since the time of Thudichum, the presentations being made by Heinrich B. Waelsch, Irvine H. Page, Jordi Folch-Pi, and J. H. Quastel. Discussion openers were Julius Axelrod, R. O. Brady, and Guilio Cantoni....The evening session was held in Washington's Cosmos

[1]Council members are: Jose Pereyra Kafer, Julio C. Ortiz de Zarate, Hugo V. Auletta, Tomas Insausti, and Alejandro J. Petre.

Club under the toastmastership of Seymour S. Kety. After the dinner, which reproduced the recipes of Thudichum, there were roundtable discussions of the horizons of neurochemistry and the dependence of other disciplines on neurochemistry. The participants, besides the toastmaster, were Jean Posternak (Geneva), Paul D. MacLean, Stephen W. Kuffler, and Joel J. Elkes.

Briefs The eighth Latin American Congress of Neurosurgery (Professor Doctor A. Asenjo, president), and the fourth South American Congress of Electroencephalography and Clinical Neurophysiology (Doctor A. Mosovich, president) will be held in Santiago, Chile (April 12-15, 1959). The neurosurgical congress will highlight a symposium on the "Cranial Nerves and Cerebellum" in which selected authors from Argentina, Bolivia, Brazil, Colombia, Mexico, Peru, and Uruguay will participate. The EEG congress will deal with current problems of EMG and EEG abnormalities and tumors of the floor of the third ventricle. Further, at the same congresses there will be a symposium on neurologic research under the direction of A. Earl Walker, devoted to ultrasonics, depth recording, cerebral circulation, and the ultrastructure of cortical neurons....Inquiries should be directed to the Secretary-General, Prof. Dr. A. Asenjo, Casilla 70 D, Santiago, Chile....Dr. Leo Madow, a member of the staff of the Institute of the Pennsylvania Hospital for Nervous and Mental Diseases and consultant in neurology at the Valley Forge Army Hospital and other hospitals, will join the faculty of the Women's Medical College of Pennsylvania as professor of neurology, July 1958....Dr. Robert A. Knight, president-elect of the American Academy for Cerebral Palsy, was killed instantly while driving with his wife and eight-year-old only son in Jackson, Mississippi (April 13, 1958). Thirty hours later his son also died of severe brain injuries. Mrs. Knight, though seriously injured, is making surprisingly good progress in a hospital in Jackson....AAN honory member, Wilder Penfield, has joined Princeton University's Institute of Advanced Studies.... Sanford Palay, a member of the branch of neuroanatomic sciences of NINDB, has been elected to present a paper on the fine structure of the mammalian central nervous system at the International Federation of Electronmicroscope Societies to be held in Berlin (September 10-17, 1958).

Percy Bailey

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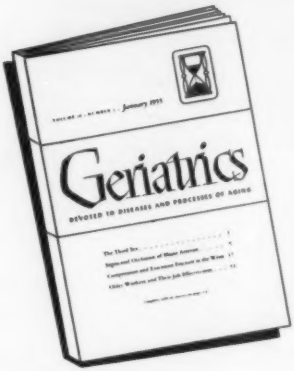

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1. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Emotional disorders treated with meprobamate and promazine. Connecticut M. J. 21:1047, Dec. 1957.

SYMPTOMATIC IMPROVEMENT

(hospitalized patients—all types)

by disease

DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
ANXIETY	30
TENSION	31
AGITATION	8
OTHERS	11
TOTAL	116

†Relief mainly in symptoms of anxiety, tension and insomnia.

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